# CLINICAL AND GENETIC ANALYSIS OF HYPERTROPHIC CARDIOMYOPATHY

***Dissertation submitted for***

THE PARTIAL FULFILLMENT OF DOCTOR OF MEDICINE

***BRANCH I – GENERAL MEDICINE***

**MARCH 2008**

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI, TAMILNADU**

## *CERTIFICATE*

This is to certify that this dissertation entitled **"CLINICAL AND GENETIC ANALYSIS OF HYPERTROPHIC CARDIOMYOPATHY "** submitted by **Dr.K.S.THIRUPATHY** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D. degree Branch I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.


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## DECLARATION

I, **Dr. K.S.THIRUPATHY** solemnly declare that I carried out this work on **"CLINICAL AND GENETIC ANALYSIS OF HYPERTROPHIC CARDIOMYOPATHY"** at Department of General Medicine, Government Rajaji Hospital during the period of March 2006 – April 2007. I also declare this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. in General Medicine Degree examination

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# ACKNOWLEDGEMENT

At the outset, I thank our Dean **Prof. Dr. RAJI M.D** for permitting me to carry out this study in our hospital.

I am grateful to our chief **Prof.Dr.S.Vadivel Murugan M.D** , professor, Department of Medicine and former chief & head of the department **Prof. Dr.Thirumalaikolundhusubramaniam M.D** for his guidance and support during this period.

I am greatly indebted to my beloved Head of the Department **Prof. Dr. A. Ayyappan M.D.,** for his guidance, encouragement and support during the study period.

I am obliged to my guide **Prof**. **Dr. R.V. Amudhan**, **M.D.,D.M., FACC.,** Additional Professor, Department of Cardiology and **Dr. Perumal Kannan**, Post graduate in Cardiology for their cooperation and valuable suggestion and Department of Cardiology.

Knowledge and kindness abounds my beloved teachers **Dr.P.Selvaraj M.D., Dr.M. Kamaraj M.D., Dr.Moses K. Daniel M.D., and Dr.D.D.Venkatraman M.D., DR. M. Muthiah M.D.** I owe them a lot and sincerely thank them.

I express my gratitude to my assistant professors **Dr.A.Senthamarai M.D, Dr.Ramakrishnan M.D, Dr.Sheela M.D, Dr.Balajinathan M.D, Dr.Dharmaraj M.D, Dr.David Pradeep Kumar M.D**,and **Dr.Senthil, M.D**. for their valuable suggestion.

I sincerely thank **Prof. Selvam P.hd** , Head of the Department, Bio Chemistry, School of Biological science, Madurai Kamaraj University and his post graduate **Mr. Perundurai Dhandapani** for cooperating with me in conducting this study.

I gratefully acknowledge to all the patients who participated in the study for their co-operation without which this work would not have been possible.

My family and friends have stood by me during my times of need. Their help and support have been invaluable to this study.

Above all I thank the Lord Almighty for His kindness and benevolence.

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# INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disease that has been the subject of intense scrutiny and investigation for more than 40 years.[1-3]Hypertrophic Cardiomyopathy is an important cause of disability and death in patients of all ages, although sudden and unexpected death in young people is perhaps the most devastating component of its natural history. Because of marked heterogeneity in clinical expression, natural history, and prognosis, HCM often represents a dilemma to primary care clinicians and cardiovascular specialists, even to those for whom this disease is a focus of their investigative careers. Controversy abounds with regard to diagnostic criteria, clinical course, and management for which difficult questions often arise, particularly among practitioners infrequently engaged in the evaluation of HCM patients. Consequently, it is timely to place in perspective and clarify many of these relevant clinical issues and profile the rapidly evolving concepts regarding HCM.

Epidemiological investigations with diverse study designs have shown similar estimates for prevalence of phenotypically expressed HCM in the adult general population at about 0.2% (1:500).[4] Therefore, HCM is not rare and is the most common genetic cardiovascular disease, with reports from many countries. Nevertheless, a substantial proportion of individuals harboring a mutant gene for HCM are probably undetected clinically. Hypertrophic cardiomyopathy is, however, uncommon in routine cardiologic practice, affecting no more than 1% of outpatients.[5]

This limited exposure of clinicians to HCM understandably accounts for the uncertainty that prevails regarding this disease and its management.

Recognition of the frequency with which hypertrophic cardiomyopathy (HC) occurs in the population is critical to understanding its demographics and public health implications. However, few data are available for estimating HC prevalence in large populations of different age strata and ethnic or racial groups.. The study population was comprised of subjects attending Cardiology Department during the period of Nov 2006-Oct 2007 to determine the prevalence of HCM in this population based on left ventricular (LV) wall thickness >/=15 mm and a nondilated cavity that was not associated with another cardiac disease and was sufficient to produce the magnitude of hypertrophy evident.

Indian study regarding HCM was limited regarding clinical manifestation, types and risk stratification. Hence this study had been put forth to review the prevalence in this part of the country, symptom analysis, clinical manifestation, types of HCM, and risk stratification for sudden death and also for genetic analysis

# REVIEW OF LITERATURE

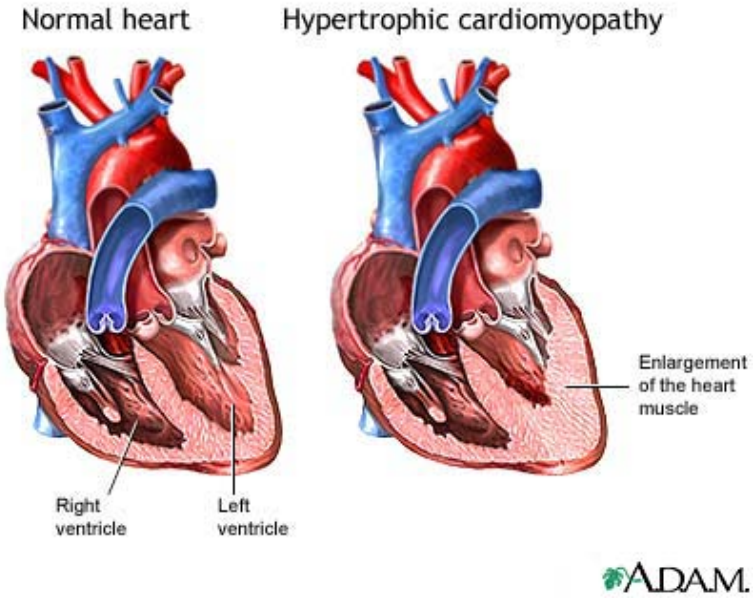
A systematic search of the medical literature involving articles primarily related to English-language HCM publications (1966-2007) from a varied and extensive number of authors and centers was reviewed through MEDLINE or bibliographies of published articles. Published accounts of HCM have come disproportionately from a relatively small group of highly selected centers in the United States, Canada, and Europe. Many clinical HCM studies are observational and retrospective in design because of difficulty in organizing large prospective and randomized clinical trials for a disease with heterogeneous expression, selective referral patterns, and diverse mechanisms for morbidity and mortality. Therefore, in HCM, the level of evidence governing management decisions is derived primarily from nonrandomized studies.

## NOMENCLATURE

Since the first modern description in 1958,[1] HCM has been known by a confusing array of names, reflecting its clinical heterogeneity and the skewed experience of early investigators.

**Hypertrophic cardiomyopathy**[7] is the preferred name because it describes the overall disease spectrum without introducing misleading inferences that left ventricular (LV) outflow tract obstruction is an invariable feature (hypertrophic obstructive cardiomyopathy [HOCM] or idiopathic hypertrophic sub aortic stenosis

[IHSS]). Indeed, HCM is predominantly a non obstructive disease; 75% of patients do not have a sizable resting outflow tract gradient.[3-4]




Clinical diagnosis of HCM is established most easily and reliably with 2-dimensional echocardiography[8] by imaging the hypertrophied but non dilated LV chamber, in the absence of another cardiac or systemic disease (e.g., hypertension or aortic stenosis) capable of producing the magnitude of hypertrophy evident.[7] Hypertrophic cardiomyopathy may be initially suspected because of a heart murmur (occasionally during preparticipation sports examinations), positive family history, new symptoms, or abnormal ECG pattern.[2]

Across the broad disease spectrum of HCM, the physical examination may not be a reliable method for clinical identification, given that most patients do not have LV outflow tract obstruction and most of the well-documented physical findings (e.g., loud systolic heart murmur and bifid arterial pulse) are limited to patients with outflow gradients.

**PATHOPHYSIOLOGY OF HYPERTROPHIC CARDIOMYOPATHY**

Although the pathology of HCM was first described by French pathologists in mid 19$^{th}$ century, it remained for virtually simultaneous reports of Brock and Teare in England 43 yrs ago to bring modern attention to this fascinating entity. Pathogenesis proposed was that In a normal person when Cardiac contraction occurs when calcium binds the troponin complex (subunits C, I, and T) and tropomyosin, making possible the myosin-actin interaction. Actin stimulates ATPase activity in the globular myosin head and results in the production of force along actin filaments. Cardiac myosin-binding protein C, arrayed transversely along the sarcomere, binds myosin and, when phosphorylated, modulates contraction. In hypertrophic cardiomyopathy, mutations may impair these and other protein interactions, result in ineffectual contraction of the sarcomere, and produce hypertrophy and disarray of myocytes. Percentages represent the estimated frequency with which a mutation on the corresponding gene causes hypertrophic cardiomyopathy

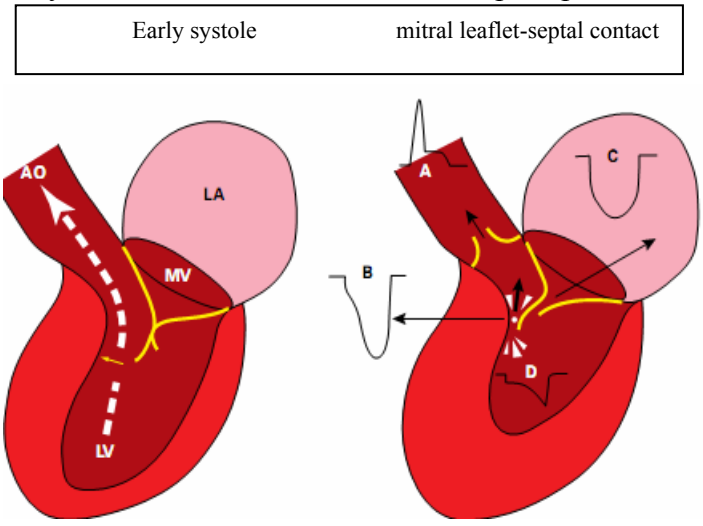
## PHYSICAL EXAMINATION:

Left ventricular involvement is reflected by a variably displaced and forceful left ventricular impulse and a left sided fourth heart sound that is often palpable, reflecting impaired left ventricular relaxation. Patients with non-obstructive HCM either have no murmur or a faint grade 1/6 systolic murmur at the cardiac apex, that does not increase significantly with provocation. In patients with latent subaortic obstruction, the murmur at the apex is usually grade 1/6 to grade 2/6 in intensity, and

increases to grade 3/6 with appropriate provocation such as amyl nitrite inhalation, assuming the upright posture from the squatting position or during the Valsalva manoeuvre.

Right ventricular involvement in HCM may be detected by prominent A wave in JVP, that rises on inspiration. A systolic ejection murmur along the high left sternal border often indicates subpulmonic or mid ventricular obstruction In patients with sub aortic obstructive HCM at rest, the murmur at or just medial to the apex is grade 3/6 to 4/6 in intensity, and begins after the first heart sound. It is harsh and crescendo/ decrescendo in character with radiation to the base of the heart, reflecting the obstruction, and to the axilla, reflecting the concomitant mitral regurgitation.

In 20% of patients with subaortic obstructive HCM there may be independent abnormalities of the mitral valve (other than systolic anterior motion) that cause mitral regurgitation such as abnormal papillary muscle insertions, mitral valve prolapse or excessive fibrotic thickening of the anterior mitral leaflet, resulting from repeated mitral leaflet–septal contact. In such cases there may also be a pansystolic murmur at the apex.On palpation there is often a bifid (spike and dome) arterial pulse, which at times has been referred to as a bisferiens pulse. A bisferiens pulse is seen in dominant aortic regurgitation. On palpation at the left ventricular apex,



there is often a double systolic impulse, the first impulse coming before the onset of the obstruction, the second after. Frequently, there is a triple apex beat, resulting from a palpable left atrial gallop sound, plus a double systolic impulse. On auscultation in subaortic obstructive HCM, there may be a reversed or paradoxically split second heart sound when the obstruction is severe or in the presence of left bundle branch block. When the mitral regurgitation is significant, it is often accompanied by a mitral diastolic inflow murmur. Rarely a mitral leaflet–septal contact sound may also be heard.

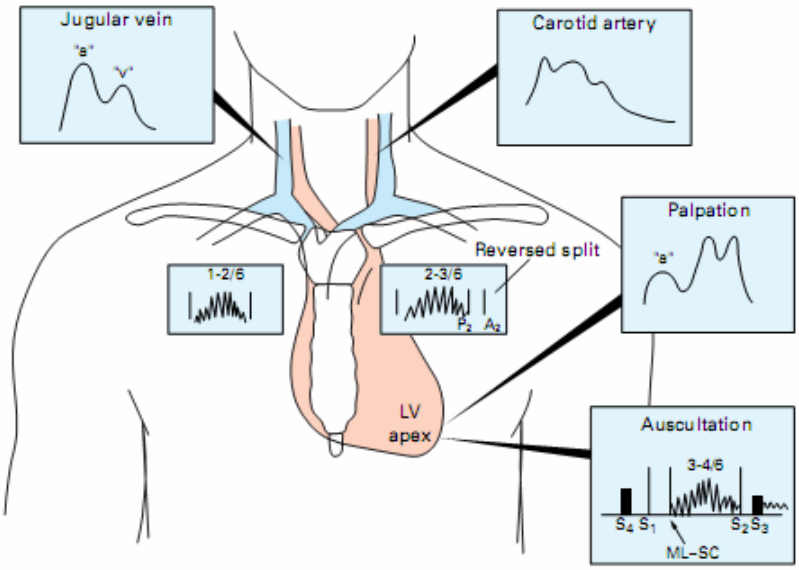



**Figure 2.** Diagram showing the seven findings on physical examination that are found in subaortic obstructive HCM and are not present in non-obstructive HCM (see text). ML-SC, mitral leaflet-septal contact sound.

*www.heartjnl.com*

Patients with midventricular obstruction also have an apical systolic murmur, although it is usually softer, grade 2/6 to 3/6, than with subaortic obstruction. A bifid arterial pulse, double systolic apex beat or triple apex beat are not characteristic of midventricular obstruction and a mitral leaflet–septal contact sound is never found. If the obstruction is severe, there may be reversed splitting of the second heart sound.

In midventricular obstruction, there is at times a very distinctive long mitral diastolic murmur, caused by the midventricular narrowing and asynchronous relaxation. In midventricular obstruction, the size of the obstructed apical cavity varies considerably. It may be quite large and haemodynamically significant or very small and more a manifestation of cavity obliteration with a small nonobliterated pocket of blood remaining at the apex. The syndrome of midventricular obstruction with apical infarction and aneurysm formation most often results from apical infarction in a patient with apical HCM in whom the non infarcted hypertrophy at the midventricular level results in midventricular obstruction.

**ELECTROCARDIOGRAPHY**

The 12-lead ECG pattern is abnormal in 75% to 95% of HCM patients and typically demonstrates a wide variety of patterns.[12] Q waves >0.04 second in duration and/or >1/3 of the ensuing R wave in depth and present in at least two leads, or left ventricular hypertrophy [24] or repolarization alterations with marked T-wave inversion in at least two leads, bundle-branch block or hemiblock with or without ST-segment displacement, Arrhythmias of all type particularly AF. Normal ECGs are most commonly encountered in family members identified as part of pedigree screening or when associated with mild localized LVH[12] .Only a modest relation between ECG voltages and the magnitude of LVH assessed by echocardiography is evident. Nevertheless, ECGs have diagnostic value in raising a suspicion of HCM in family members without LVH on echocardiogram and in targeting athletes for diagnostic echocardiography as part of preparticipation screening.

## ECHOCARDIOGRAPHY

In clinically diagnosed patients, increased LV wall thicknesses range widely from mild (13-15 mm)[3,] to massive (≥30 mm [normal, ≤12 mm]),[10,] including the most substantial in any cardiac disease, namely, up to 60 mm [40] In trained athletes, modest segmental wall thickening (i.e., 13-15 mm) raises the differential diagnosis between extreme physiologic LVH (i.e., athlete's heart) and mild morphologic expressions of HCM, which can usually be resolved with noninvasive testing. Magnetic resonance imaging may be of diagnostic value when echocardiographic studies are technically inadequate or in identifying segmental LVH undetectable by echocardiography.

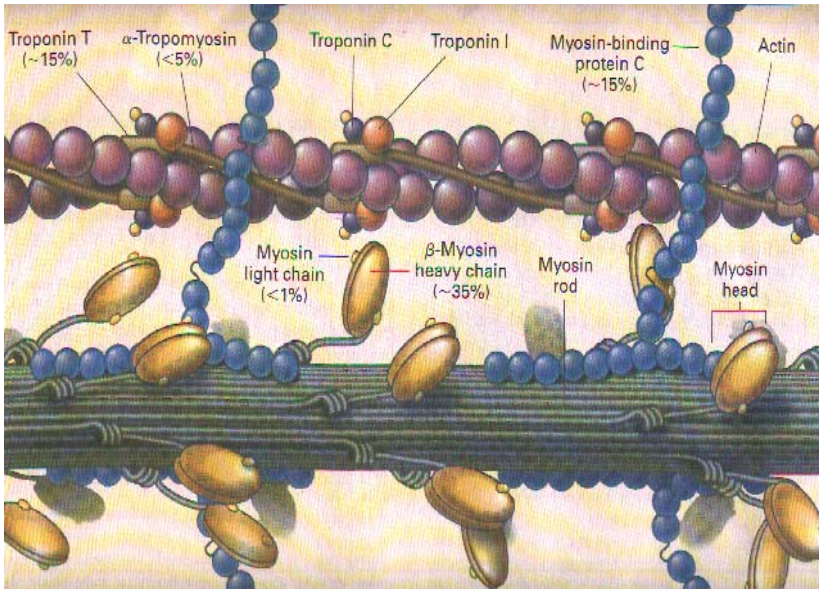
Based on Echo HCM can be classified as Left ventricular, Right ventricular. In the left ventricular type it may be asymmetrical or concentric. The approximate incidence of types of HCM[46]

| Types of HCM | Incidence % |
|---|---|
| Left ventricular involvement | |
| Asymmetrical Hypertrophy | 95 |
| Septal | 80 |
| Apical | 9 |
| Midventricular | 4 |
| Rare types | 2 |
| Symmetrical(conc.) Hypertrophy | 5 |
| Right ventricular involvement | - |

*Toronto General Hospital[46]

## GENETICS

Hypertrophic Right ventricular involvement in HCM may be detected by prominent A wave in JVP, that rises on inspiration. A systolic ejection murmur along the high left sternal border often indicates subpulmonic or mid ventricular obstruction cardiomyopathy is inherited as a mendelian autosomal dominant trait and caused by mutations in any 1 of 10 genes, each encoding proteins of the cardiac sarcomere (components of thick or thin filaments with contractile, structural, or regulatory functions).[13](Figure 4) The physical similarity of these proteins makes it possible to regard the diverse HCM spectrum as a single disease entity and primary sarcomere disorder. The mechanisms by which disease-causing mutations cause LV hypertrophy (LVH) and the HCM disease state are unresolved, although several hypotheses have been suggested.[14]




Three of the HCM-causing mutant genes predominate, namely, β-myosin heavy chain (the first identified), cardiac troponin T, and myosin-binding protein C. The other genes each account for a minority of HCM cases, namely, cardiac troponin I, regulatory and essential myosin light chains, titin, α-tropomyosin, α-actin, and α-myosin heavy chain. This diversity is

compounded by intragenic heterogeneity, with more than 150 mutations identified, most of which are missense with a single amino acid residue substituted with another.[13] Molecular defects responsible for HCM are usually different in unrelated individuals, and many other genes and mutations, each accounting for a small proportion of familial HCM, remain to be identified.

PCR was the technique used for genetic analysis. THE POLYMERASE CHAIN REACTION The PCR, introduced in 1985, has revolutionized the way DNAanalyses are performed and has become a cornerstone of molecular biology and genetic analysis. In essence, PCR provides a rapid way of cloning (amplifying) specific DNAfragments in vitro (Fig. 56-7). Exquisite specificity is conferred by the use of PCR primers, which are designed for a given DNAsequence. The geometric amplification of the DNAafter multiple cycles yields remarkable sensitivity. As a result, PCR can be used to amplify DNA from very small samples, including single cells. These properties also allow DNAamplification from a variety of tissue sources including blood samples, biopsies, surgical or autopsy specimens, or cells from hair or saliva. PCR can also be used to study mRNA. In this case, the enzyme RT is first used to convert the RNAto DNA, which can then be amplified by PCR. This procedure, commonly known as RT-PCR, is useful as a quantitative measure of gene expression. PCR provides a key component of molecular diagnostics. It provides a strategy for the rapid amplification of DNA(or mRNA) to search for mutations by a wide array of techniques, including DNA sequencing. PCR is also used for the amplification of highly polymorphic di- or trinucleotide repeat sequences, which allow various

polymorphic alleles to be traced in genetic linkage or association studies. PCR is increasingly used to diagnose various microbial pathogens.

Contemporary molecular genetic studies throughout the past decade have provided important insights into the considerable clinical heterogeneity of HCM, including the preclinical diagnosis of affected individuals without phenotypic evidence of disease (ie, LVH by echocardiography or electrocardiography [ECG]).[12] Although **DNA analysis for mutant genes is the definitive method for establishing the diagnosis of HCM, it is not yet a routine clinical strategy.**[13] Because of complex, time-consuming, and expensive techniques, genotyping is confined to research-oriented investigations of highly selected pedigrees. Development of rapid automated screening for genetic abnormalities will permit more widespread access to the power of molecular biology for resolving diagnostic ambiguities.

Recently, missense mutations in the gene that encodes the γ-2 regulatory subunit of the adenosine monophosphate–activated protein kinase (*PRKAG2*) have been reported to cause familial Wolff-Parkinson-White syndrome associated with conduction abnormalities and LVH[15] (because of glycogen accumulation in myocytes).[15] This syndrome is most appropriately regarded as a metabolic storage disease distinct from HCM, which is caused by mutations in genes encoding sarcomeric proteins. Therefore, management and risk assessment of patients with Wolff-Parkinson-White syndrome and cardiac hypertrophy should not be predicated on data derived from patients with HCM.

Of potential importance for understanding HCM pathophysiology are genetic animal models (ie, transgenic mice and rabbits)[15] and spontaneously occurring animal diseases.[15] In particular, domestic cats with heart failure commonly show a disease with clinical and morphologic features remarkably similar to HCM in humans.[15]

it has become clear more recently that the link between genotype and risk is not simple. First, Ackerman and colleagues examined the prevalence of several mutations in a population of 293 HCM patients at a tertiary referral centre (Mayo Clinic). Mutations previously reported to be "malignant" (MYH7 and TNNT2) were found in only three (1%) of the 293 patients. Second, there may be wide phenotypic variation (including natural history) between affected individuals within the same family, let alone between different families sharing the same genotype. For example, in a large Scottish family with HCM caused by a TNNT2 mutation, eight affected members died suddenly age < 30 years, whereas eight other affected members survived into old age.[25] Explanations proposed to explain this phenotypic variability include: compound heterozygosity, modifier genes, epigenetic factors (DNA methylation and imprinting), epistasis (interaction between genes), post-transcriptional and post-translational modifications of gene products, presence of coexisting diseases, and environmental influences.

**DIAGNOSIS**

Novel diagnostic criteria for HCM have recently emerged and are based on genotype-phenotype studies showing incomplete disease expression with absence of

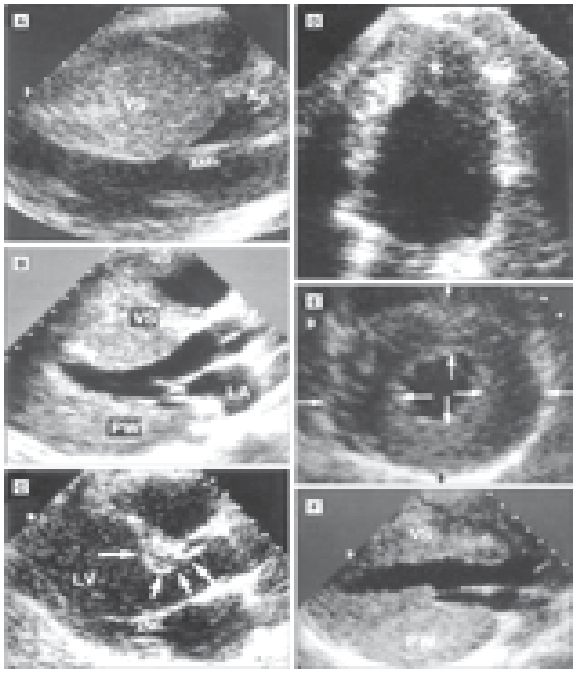
LVH in adult individuals, most commonly due to cardiac myosin-binding protein C or troponin T mutations.[13] In both cross-sectional and serial echocardiographic studies, mutations in the myosin-binding protein C gene may demonstrate age-related penetrance of the HCM phenotype in which delayed de novo onset of LVH may occur in midlife and later.[13] Such adult morphologic conversions dictate that it is no longer possible to use a normal echocardiogram to offer definitive reassurance at maturity (or even in middle age) that asymptomatic family members are free of a disease-causing mutant HCM gene[13] .This observation probably necessitates a strategy of postadolescent echocardiographic examinations every 5 years.

Paradoxically, a small distinctive subset of HCM patients (i.e., about 5%-10%) evolve into the end stage (or "burned-out" phase) characterized by LV wall thinning, cavity enlargement, and systolic dysfunction often resembling dilated cardiomyopathy and producing relentlessly progressive and irreversible heart failure.[3] It is also possible that other adults experience subtle regression in wall thickness with aging (not linked with clinical deterioration), reflecting gradual, widespread remodeling. Therefore, the HCM phenotype is not a static disease manifestation; LVH can appear at virtually any age and increase or decrease dynamically throughout life.

## HCM PHENOTYPE AND MORPHOLOGIC FEATURES

**Left Ventricular Hypertrophy.** Structural heterogeneity in HCM is considerable, with no single pattern of LVH regarded as typical (Figure 5) .[3] Although many patients show diffusely distributed LVH, almost one third have mild wall thickening localized

to a single segment, including the apical form[16] that appears most commonly in Japanese people. Left ventricular hypertrophy is characteristically asymmetric, with the anterior septum usually predominant (Figure 5A-D, Figure 5F), although a few patients show a symmetric (concentric) pattern (Figure 1E).



**Echo showing Hypertrophic cardiomyopathy**

Figure (A-D, F): Asymmetric septal Hypertrophy

Figure (E) : Concentric

Distribution of LV wall thickening shows no direct linkage to outcome, although distal hypertrophy is associated with the absence of obstruction. Young children may present with LVH resembling HCM as part of other disease states (e.g., Noonan syndrome, mitochondrial myopathies, and metabolic disorders) unrelated to HCM-causing sarcomere protein mutations. Other markers of HCM that are not obligatory prerequisites for diagnosis include a hypercontractile LV and dynamic subaortic obstruction typically produced by mitral valve systolic anterior motion and

septal contact[17] (caused by drag effect[18] or possibly the Venturi phenomenon[17]), which is responsible for a loud systolic murmur.

The sudden deceleration of longitudinal septal motion might be caused by an external force, pushing or dragging the septum towards the base. However, this cannot be explained by the LVOT gradient itself, which develops in parallel to the septum. Alternatively, it might be caused by an internal unbalance of myocardial forces within the septum. Normal systolic radial and longitudinal myocardial thickening occurs almost simultaneously. Dynamic LVOT obstruction leads to a sudden rise in LV pressure during mid systole. The excessive rise in LV wall stress will impede further myocardial thickening in the radial direction and this will also hamper longitudinal shortening caused by the conservation of mass principle. The only segment which is not affected by the abnormally increased LV cavity pressure is the basal septal myocardial segment which lies below (downstream to) the region of mitral septal contact, thus being exposed to a lower mid systolic wall stress.[5] Isolated longitudinal shortening of this basal septal segment will drag the septum towards the base, thereby causing the MSSD (mid systolic septal deceleration) notch. This abnormal septal motion may contribute further to LVOT narrowing and the positive amplifying feedback loop of LVOT obstruction.

## LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION:

A recent large study reported that patients with a resting peak instantaneous outflow tract gradient > 30 mm Hg were at increased risk of total mortality (RR 2.0, 95% CI 1.3 to 3.0), of death from heart failure or stroke (RR 4.4, 95% CI 3.3 to 5.9),

and of SCD (RR 2.1, 95% CI 1.1 to 3.7). There was no evidence of increasing risk with progressively increasing gradients above this threshold.[49] The negative predictive accuracy for SCD was very high (95%) but the positive predictive accuracy was very low (7%). The impact of treatments aimed at reducing outflow tract obstruction (medical, surgical, and alcohol septal ablation) on the risk of SCD has not been formally assessed.

**Cellular Components:** Cardiomyopathic substrate in HCM is defined anatomically by several histological features based on autopsy observations. Left ventricular myocardial architecture is disorganized, composed of hypertrophied cardiac muscle cells (myocytes) with bizarre shapes and multiple intercellular connections often arranged in chaotic alignment at oblique and perpendicular angles (Figure 2B).[1] Cellular disarray may be widely distributed, occupying substantial portions of LV wall (average, 33%), and is more extensive in young patients who die of their disease.

Abnormal intramural coronary arteries, characterized by thickened walls with increased intimal and medial collagen and narrowed lumen, may be regarded as a form of small vessel disease (Figure 2). Such architectural alterations of the microvasculature, as well as the mismatch between myocardial mass and coronary circulation, are likely responsible for impaired coronary vasodilator reserve[19] and bursts of myocardial ischemia[19]leading to myocyte death and repair in the form of patchy or transmural replacement scarring (Figure 2).[19] Such myocardial scarring supports clinical evidence that ischemia frequently occurs within the natural history of HCM[19] and may serve as the substrate for premature heart failure–related death. It is

also evident that the cardiomyopathic process in HCM is not confined to areas of gross wall thickening and that nonhypertrophied regions also contribute to ischemia or impaired diastolic function.[20]

Disorganized cellular architecture,[1] myocardial scar-ring,[19] and expanded interstitial (matrix) collagen probably serve as arrhythmogenic substrates predisposing to life-threatening electrical instability. This substrate is likely the source of primary ventricular tachycardia and ventricular fibrillation, which appear to be the predominant mechanisms of sudden death,[21] either primarily or in association with triggers intrinsic to the disease process, namely, myocardial ischemia, systemic hypotension, supraventricular tachyarrhythmias, or environmental variables (eg, intense physical exertion).

Penetrance and variability of phenotypic expression are undoubtedly influenced by factors other than disease-causing mutant genes such as modifier genes (e.g., angiotensin-converting enzyme genotype),[22] coexistent hypertension, or lifestyle. Indeed, several phenotypic manifestations of HCM do not primarily involve sarcomeric proteins, including increased interstitial collagen, abnormal intramural arteries, and mitral valve malformations such as elongated leaflets or direct papillary muscle insertion into the mitral valve.

## CLINICAL COURSE

Hypertrophic cardiomyopathy is unique among cardiovascular diseases by virtue of its potential for clinical presentation during any phase of life (from infancy to >90 years of age).[1-3,22] Although adverse clinical consequences have been recognized for many years, particularly sudden cardiac death,[1,2] a more balanced perspective regarding prognosis has evolved recently.[23]

Historically, misperceptions regarding the clinical significance of HCM have prevailed because of its relatively low prevalence in cardiac populations, extreme heterogeneity, and skewed patterns of patient referral that created important selection biases.[23] Indeed, much of the data assembled throughout the past 40 years have been disproportionately generated by a few tertiary centers largely composed of patients preferentially referred because of their high-risk status or severe symptoms requiring specialized care such as surgery.[23] Hence, the older literature was dominated by the most adverse consequences of HCM, while clinically stable, asymptomatic, and elderly patients were underrepresented.

Consequently, the risks of HCM would appear to have been overestimated by dependence on frequently cited, ominous mortality rates of 3% to 6% annually.[24]. Recent reports throughout the last 7 years from less selected regional or community-based HCM patient cohorts cite much lower annual mortality rates, about 1%,[25] not dissimilar to that for the general adult US population.[23] Such data provide a more balanced view in which HCM may be associated with important symptoms and

premature death but more frequently with no or relatively mild disability and normal life expectancy.

Elderly HCM patients (≥75 years) have been reported to compose as much as 25% of an HCM cohort, with only a minority having severe manifestations of heart failure.[23] Outflow obstruction is commonly evident in patients of advanced age (ie, in about 40%), suggesting that subaortic gradients may be well tolerated for long periods without adverse consequences. Indeed, HCM in elderly patients can be a genetic disorder caused by dominant sarcomere protein mutations most commonly in cardiac myosin-binding protein C and troponin I genes.[26]

## PROFILES OF PROGNOSIS AND TREATMENT STRATEGIES

The clinical course for individual HCM patients is most appropriately viewed in terms of specific subgroups rather than only from perceptions of the overall disease spectrum. Some patients progress along certain relatively discrete, adverse pathways: (1) high risk for sudden death[1-3] (2) congestive symptoms of heart failure with exertional dyspnoea and functional disability often associated with chest pain and usually in the presence of preserved LV systolic function[23]; and (3) consequences of atrial fibrillation (AF),[27] including embolic stroke.

**Sudden Death** *Risk Stratification.* Sudden death is the most common mode of demise and the most devastating and unpredictable complication of HCM.[1-3] Therefore, within

the broad HCM disease spectrum, for which overall annual mortality rate is about 1%, exist small subsets at a much higher risk (perhaps at least 5% annually).

An important but complex objective has been the identification of such higher-risk individuals among the vast HCM spectrum. For example, sudden death can be the initial manifestation of HCM, and such patients usually have no or only mild prior symptoms.

Indeed, HCM is the most common cause of cardiovascular sudden death in young people, including trained competitive athletes (most commonly in basketball and football and in black athletes).[28]

Highest risk for sudden death in HCM has been associated with any of the following noninvasive clinical markers[3,23] prior cardiac arrest or spontaneous sustained ventricular tachycardia; family history of premature HCM-related death, particularly if sudden, in close relatives, or multiple; syncope and some cases of near-syncope, particularly when Exertional or recurrent, or in young patients when documented as arrhythmia-based or clearly unrelated to neurocardiogenic mechanisms; multiple and repetitive or prolonged bursts of nonsustained ventricular tachycardia on serial ambulatory (Holter) ECG recordings; hypotensive blood pressure response to exercise, particularly in patients younger than 50 years; and extreme LVH with maximum wall thickness ≥30 mm, particularly in adolescents and young adults.

**Table 3** Annual sudden cardiac death rates together with their 95% confidence intervals (CIs) from seven selected natural history studies in which calculation of different rates was possible depending on inclusion or exclusion of resuscitated cardiac arrest (CA) and appropriate ICD discharges as end points

| Author and date | Criteria | SD rate (95% CI) |
|---|---|---|
| Maron[20] 1981 | | |
| Authors' criteria | Including 2 CA (ie) | 2.0 (0.74 to 4.40) |
| Recalculation | Excluding 2 CA (ie) | 1.3 (0.37 to 3.45) |
| Kofflard[31] 1993 | | |
| Authors' criteria | Including 1 CA (dx) | 1.1 (0.5 to 2.07) |
| Recalculation | Excluding 1 CA (dx) | 1.0 (0.42 to 1.91) |
| Cannan[32] 1995 | | |
| Authors' criteria | Including 2 CA (ie) | 1.1 (0.22 to 3.12) |
| Recalculation | Excluding 2 CA (ie) | 0.4 (0.01 to 1.98) |
| Maron[8] 1999 | | |
| Authors' criteria | Excluding 3 CA, and 3 ICD (dx) | 0.8 (0.44 to 1.21) |
| Recalculation | Including 3 CA (dx) | 0.9 (0.54 to 1.38) |
| | Including 3 CA and 3 ICD (dx) | 1.0 (0.65 to 1.54) |
| Maron[9] 2000 | | |
| Authors' criteria | Including 11 CA and 3 ICD (ie/dx) | 0.7 (0.54 to 0.99) |
| Recalculation | Excluding 3 ICD (ie/dx) | 0.7 (0.49 to 0.93) |
| | Excluding 3 ICD and 11 CA (ie/dx) | 0.5 (0.34 to 0.72) |
| Spirito[24] 2000 | | |
| Authors' criteria | Excluding 3 CA and 3 ICD (ie/dx) | 0.7 (0.47 to 1.11) |
| Recalculation | Including 3 CA (ie/dx) | 0.8 (0.54 to 1.22) |
| | Including 3 CA and 3 ICD (ie/dx) | 0.9 (0.62 to 1.33) |
| Elliott[19] 2001 | | |
| Authors' criteria | Including 4 ICD (ie) | 1.3 (0.90 to 1.73) |
| Recalculation | Excluding 4 ICD (ie) | 1.1 (0.79 to 1.58) |
| SGH 1988–2002 | | |
| Authors' criteria | Including 4 CA and 8 ICD (ie) | 1.0 (0.76 to 1.26) |
| Recalculation | Including 4 CA and 8 ICD (dx) | 0.6 (0.43 to 0.74) |
| | Excluding 8 ICD (ie) | 0.9 (0.64 to 1.16) |
| | Excluding 8 ICD (dx) | 0.5 (0.36 to 0.64) |
| | Excluding 8 ICD and 4 CA (ie) | 0.8 (0.58 to 1.07) |
| | Excluding 8 ICD and 4 CA (dx) | 0.4 (0.32 to 0.60) |

dx, follow up started from diagnosis of hypertrophic cardiomyopathy; ie, follow up started from initial evaluation.

There is only a suggested association[23] but no clinically relevant and independent linkage between sudden death and outflow obstruction,[3,23] although data on particularly large (≥100 mm Hg) gradients are limited.[23] One report suggests that short, tunneled (bridged) segments of left anterior descending coronary artery, mediated by ischemia, independently convey increased risk for cardiac arrest in children with HCM.[29]

Presentation of HCM in young children is exceedingly uncommon and usually creates a clinical dilemma because of diagnosis (often fortuitous) so early in life and the uncertainty regarding risk over such long periods. Studies of HCM in children report annual mortality rates of 2% (community-based populations) to 6% (tertiary referral cohorts).

It has been proposed, based on genotype-phenotype correlations, that the genetic defects responsible for HCM[3,23,29] could represent the primary determinant and stratifying marker for sudden death risk, with specific mutations conveying either favorable or adverse prognosis. For example, some β-myosin heavy chain mutations (e.g., Arg403Gln and Arg719Gln) and some troponin T mutations may be associated with a higher frequency of premature death compared with other mutations, such as those of myosin-binding protein C (InsG791) or α-tropomyosin (Asp175Asn).[3,13,16] However, caution is warranted before strong conclusions are drawn regarding prognosis based solely on the available epidemiologic genetic data. Access to the molecular biology of HCM does not yet represent a clinically relevant strategy that routinely affects disease management.

Although attention has understandably focused on high-risk HCM patients, the absence of risk factors and certain clinical features can be used to develop a profile of HCM patients at low likelihood for sudden death caused by life-threatening rhythm disturbances, as well as other adverse events (e.g., at a rate of <1% annually). Such patients with favorable prognosis constitute an important proportion of the overall

HCM population and generally deserve a measure of reassurance regarding their disease.[3]

Most HCM patients should undergo a risk stratification assessment (probably with the exception of patients older than 60 years) that requires, in addition to careful history taking and physical examination, noninvasive testing with 2-dimensional echocardiography, 24- or 48-hour ambulatory Holter ECGs, and treadmill (or bicycle) exercise testing. Such evaluation and follow-up should be carried out by (or involve) qualified specialists in cardiovascular medicine.

Two groups recently reported that extreme LVH (maximum wall thickness > 30 mm) was associated with an increased risk of SCD during follow up.[50]

The other group (McKenna and colleagues) confirmed that patients with maximum wall thickness > 30 mm had a higher probability of SCD or AICD discharge than those with maximum wall thickness < 30 mm (RR 2.07, 95% CI 1.00 to 4.25).

Severe LVH is a risk factor for SCD but its predictive accuracy is low—sensitivity 26%, specificity 88%, positive predictive accuracy 13%, and negative predictive accuracy 95%.[51].

McKenna and colleagues have shown convincingly that consideration of the overall burden of risk factors considerably improves the predictive accuracy. They considered four variables (ABPR, maximum wall thickness > 30 mm, NSVT, and the "combined variable" of family history of SCD in at least one relative < 45 years and history of syncope) in a group of 368 consecutive patients. The estimated six year

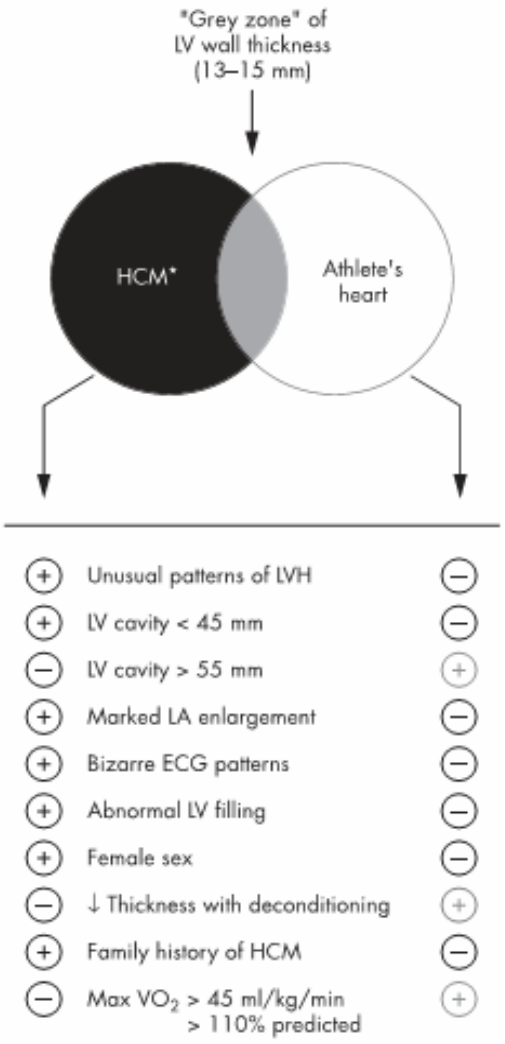



**Figure 1** Criteria used to distinguish hypertrophic cardiomyopathy (HCM) from athlete's heart when the left ventricular (LV) wall thickness is within the shaded "grey zone" of overlap, consistent with both diagnoses. ↓ indicates decreased; LA, left atrial; LVH, left ventricular hypertrophy. Reproduced from Maron *et al*,[11] with permission of American Heart Association.

SCD-free survival rates according to the number of risk factors present were as follows: 0 (n = 203), 95% (CI 91% to 99%); 1 (n = 122), 93% (CI 87% to 99%); 2 (n = 36), 82% (CI 67% to 96%); 3 (n = 7), 36% (CI 0% to 75%).

Important differential diagnosis of LVH is athletic heart. Flow chart above differentiates the clinical features.

**Prevention:** In HCM, treatment strategies to reduce risk for sudden death have been historically predicated on drugs such as β-blockers, verapamil, and antiarrhythmic agents (ie, quinidine, procainamide, and amiodarone). Nevertheless, there is little evidence[30] that prophylactic pharmacological strategies and rhythm-modulating drugs

effectively reduce risk for sudden death; furthermore, because of its potential toxicity, amiodarone is unlikely to be tolerated throughout the long risk periods characteristic of young HCM patients.

At present, the implantable cardioverter-defibrillator (ICD) appears to be the most effective treatment modality for the high-risk HCM patient, with the potential to alter natural history[22] .In a large multicenter study, ICDs aborted potentially lethal ventricular tachyarrhythmias and restored sinus rhythm in almost 25% of patients throughout a brief 3-year follow-up. Appropriate device interventions occurred at 11% annually for secondary prevention (implant following cardiac arrest) and 5% annually for primary prevention (implant based on risk factors), usually in patients with no or only mild prior symptoms. Patients receiving appropriate shocks were young (mean, 40 years), and ICDs often remained dormant for prolonged periods before discharging (up to 9 years), emphasizing the unpredictability of sudden death events in HCM.

Sudden death prevention with the ICD is most strongly warranted for patients with prior cardiac arrest or sustained spontaneous ventricular tachycardia. Although multiple risk factors convey increasingly greater sudden-death risk,[31] a single major risk factor in an individual patient may be sufficient to justify strong consideration for primary prevention with an ICD.. Also, physician and patient attitudes toward ICDs (and also access to the devices) can vary considerably among countries and cultures and profoundly affect clinical decision making.

Intense physical exertion constitutes a sudden-death trigger in susceptible individuals.[28] Therefore, to reduce risk, disqualification of athletes with unequivocal evidence of HCM from most competitive sports has been prudently recommended by a national consensus panel.[32]

**Atrial Fibrillation:** Atrial fibrillation is the most common sustained arrhythmia in HCM, accounting for unexpected hospital admissions and unscheduled work loss, and therefore usually justifies aggressive therapeutic strategies. Paroxysmal episodes or chronic AF ultimately occur in 20% to 25% of HCM patients, increase in incidence with age, and are linked to left atrial enlargement.[23] Atrial fibrillation is reasonably tolerated by about one third of patients and is not an independent determinant of sudden death.[33]

However, AF is associated with embolic stroke (incidence, about 1% annually; prevalence, 6%), leading to death and disability most frequently in the elderly,[33]as well as progressive heart failure, particularly when AF onset occurs before 50 years of age and is associated with basal outflow obstruction.[33]

Paroxysmal AF may be responsible for acute clinical decompensation, requiring electrical or pharmacological cardioversion.[34] Although data in HCM patients are limited, amiodarone is regarded as effective for reducing AF recurrences. In chronic AF, β-blockers and verapamil effectively control heart rate, although A-V node ablation with permanent ventricular pacing may occasionally be necessary. Because of the potential for clot formation and embolization, anticoagulant therapy

with warfarin is indicated in patients with either recurrent or chronic AF. Since 1 or 2 paroxysms of AF have been associated with the risk for systemic thromboembolism in HCM, the threshold for initiation of anticoagulant therapy should be low.[33] However, such clinical decisions should be tailored to the individual patient after the obligatory lifestyle modifications, risk of hemorrhagic complications, and expectations for compliance have been considered.

**Heart Failure:** *Presentation.* Symptoms such as exertional dyspnoea, orthopnea, paroxysmal nocturnal dyspnoea, and fatigue are common, characteristically in the presence of normal or supranormal LV contractility and independent of whether outflow obstruction is present .Such symptoms of HCM-related heart failure are usually deferred until adulthood but may occur at any age.

Marked symptom progression (to New York Heart Association classes III and IV) is relatively infrequent, developing in about 15% to 20% of an unselected population, and such exertional disability may evolve at varying rates; deterioration is often gradual and punctuated with long periods of stability and day-to-day variability[3]

Congestive symptoms and exertional limitation in HCM appear to be largely the consequence of diastolic dysfunction in which impaired LV relaxation, increased chamber stiffness, and compromised left atrial systolic function impede filling, leading to elevated left atrial and LV end-diastolic pressures with reduced stroke volume and cardiac output. These mechanisms result in pulmonary congestion with diminished exercise performance[35] evidenced by reduced peak oxygen consumption. However,

heart failure related to diastolic dysfunction may also be intertwined with other pathophysiological mechanisms such as myocardial ischemia, outflow obstruction, and AF.[3,33]

Chest pain suggestive of myocardial ischemia (with angiographically normal coronary arteries), either typical or atypical of angina, is a symptom commonly associated with exertional dyspnea.[3] Myocardial perfusion defects, net lactate release during atrial pacing, and blunted coronary flow reserve constitute evidence of ischemia likely caused at least in part by an abnormal microvasculature.[19] The role of ischemia in risk stratification is unresolved, in part because the clinical assessment of ischemia (and that of diastolic dysfunction) have been limited by an inability to noninvasively measure these abnormalities with quantitative precision.

**Drug Treatment Strategies:** If exertional symptoms of heart failure intervene, it is conventional to initiate pharmacological therapy with negative inotropic drugs such as β-adrenergic blockers or verapamil, independent of whether outflow obstruction is present[3,34] .Patients who do not experience improvement of symptoms with one drug may subsequently benefit from the other, but combined administration is not advantageous.[34] However, verapamil may be deleterious to some patients with severe outflow gradients and heart failure,[17] and some investigators favor disopyramide (often with a β-blocker) for such severely symptomatic patients with obstruction and verapamil or β-blockers in patients who do not develop obstruction. There are comparatively few data available regarding the use of other calcium channel blockers such as diltiazem in HCM for relief of symptoms. Patients who develop severe

symptoms of heart failure associated with systolic dysfunction and deteriorate into the end stage require alternative drug treatment with diuretics, vasodilators, and digitalis.[3,34]

β-Blockers may mitigate predominantly provocable gradients (induced with interventions such as physiologic exercise or Valsalva maneuver, isoproterenol infusion, or amyl nitrite inhalation),[2] and disopyramide may reduce some subaortic gradients at rest,[36] mediated by ventricular afterload reduction and slowing of the LV ejection acceleration.[36] For patients with outflow obstruction, risk for bacterial endocarditis (usually involving the mitral valve) dictates prophylactic administration of antimicrobial drugs, primarily to patients with obstruction, before dental procedures or surgery.

**Surgical Treatment.** Should severe heart failure–related symptoms become unrelenting and refractory to pharmacological treatment, and lifestyle unacceptable, subsequent therapeutic decisions are determined largely by whether basal obstruction to LV outflow is present (peak instantaneous gradient ≥50 mm Hg[3] Throughout the past 40 years, the experience of many centers worldwide has caused the ventricular septal myotomy-myectomy operation (Morrow procedure) to become established as the standard therapeutic option (i.e., "gold standard") for adults and children with obstructive HCM and severe drug-refractory symptoms.[3,17] However, operative candidates represent only a small (5%) although important subset of the overall HCM population.

Operation requires resection of a small amount of muscle (about 5 g) from the proximal septum extending just beyond the distal margins of mitral leaflets, thereby abolishing any significant impedance to LV outflow.[37] Other surgeons have used a low-profile mitral valve prosthesis in patients judged to have unfavorable septal morphology or with intrinsic mitral valve disease (such as myxomatous degeneration) accounting for severe mitral regurgitation.

Myotomy-myectomy performed at experienced surgical centers in the absence of associated conditions has acceptably low operative mortality (≤2%). Most patients (about 70%) achieve subjective improvement in symptoms and exercise capacity 5 years or longer after their operation and often for extended periods. Consistent relief of severe symptoms following surgery is evidence that marked outflow gradients and increased LV systolic pressure are of clinical significance to many patients. However, outflow obstruction is not deleterious to all patients, since it is now evident that large gradients may be tolerated for long periods with no or little disability.[23] Consequently, although the outflow gradient is a highly visible and quantifiable component of HCM, it is also typically labile and hemodynamically sensitive to alterations in ventricular volume and systemic vascular resistance,[2] even after standing or a heavy meal, and should not be regarded as equivalent to the disease itself. Although major interventions can be advantageous by reducing the outflow gradient when it is judged to be persistent and the cause of severe symptoms, the presence per se of subaortic obstruction unassociated with marked disability is rarely the sole justification for such treatment.

**Alternatives to Surgery.** Some operative candidates may not have ready access to major centers experienced with myotomy-myectomy because of geographical factors, or they may not be regarded as favorable operative candidates because of concomitant medical conditions, advanced age, prior cardiac surgery, or insufficient motivation.

Chronic dual-chamber pacing was associated with amelioration of symptoms and reduction of outflow gradient in many HCM patients.[38] However, several randomized crossover clinical trials reported that subjective symptomatic benefit during pacing frequently occurs with little objective evidence of improved exercise capacity and can be largely explained as a placebo effect.[38] While myotomy-myectomy provides superior results to pacing in most patients, a dual-chamber pacing trial prior to myotomy-myectomy could be of value in selected candidates, given that pacing (1) is implicitly less invasive than surgery or alcohol septal ablation, (2) is a more widely accessible method to the practicing cardiologist, (3) can permit more aggressive drug treatment by obviating concern for drug-induced bradycardia, (4) may be withdrawn, and (5) does not obviate subsequent implementation of invasive procedures. Pacing does not reduce sudden-death risk significantly[38] or trigger LV remodeling.

A second alternative therapy -alcohol septal ablation technique, which is a percutaneous coronary artery intervention using methods and technology available for atherosclerotic coronary artery disease.[39] Absolute alcohol (about 1-4 mL) is introduced into the target septal perforator coronary artery branch to produce myocardial infarction, which in turn reduces basal septal thickness and motion, enlarges the LV outflow tract, and decreases mitral valve systolic anterior motion,

thereby mimicking the hemodynamic consequences of myotomy-myectomy.[39] Indeed, reductions in outflow gradient associated with alcohol septal ablation have been reported to be similar to those resulting from myotomy-myectomy. Also, similar proportions of ablation and surgical patients have been reported to show subjective[39] and objective improvements in congestive symptoms and quality of life over relatively short periods, largely in observational studies; in addition, there are unconfirmed claims of diffuse regression of LVH following ablation. However, alcohol septal ablation in HCM has not yet been subjected to the scrutiny of randomized or controlled studies.[38]

Septal ablation is associated with operative morbidity and mortality, similar to that of myotomy-myectomy; complications include permanent pacemaker for high-grade A-V block, coronary dissection, and large anterior infarction.[39] In contrast to that for surgery, the postprocedural follow-up for alcohol septal ablation is relatively brief (about 3-5 years compared with 40 years for myotomy-myectomy).

**Heart Transplantation.** Therapeutic options are considerably limited for patients who have the nonobstructive form of HCM and experience drug-refractory severe symptoms, including those in the end-stage phase. This subset of patients, among the broad HCM spectrum, may become candidates for heart transplantation.[40]

# AIM AND OBJECTIVE

The aim and objective of our study was to know the Prevalence of hypertrophic cardiomyopathy among the patients of Government Rajaji Hospital within the study period and to compare with the world's prevalence rate.

Symptom and Clinical manifestations of hypertrophic cardiomyopathy cases were to be reviewed based on their age of presentation and sex. To review the various presentation of electrocardiograph related to rate, rhythm, axis, Left atrial hypertrophy, Left ventricular Hypertrophy.

Echocardiographic features of each case to be analyzed based on the left ventricular hypertrophy, outflow tract obstruction, types of hypertrophic cardiomyopathy.

The aim was also to risk stratify based on the symptoms, past history and clinical findings. With the help of Kamaraj University, HCM cases to be genetically analyzed for mutations in common genes related to HCM.

# MATERIALS AND METHOD

**SETTING** **:** Department of Medicine, Government Rajaji Hospital, Madurai

**COLLABORATING DEPARTMENT:** Department of Cardiology, Government Rajaji Hospital, Madurai

**ETHICAL APPROVAL** **:** The present project was approved by the ethical Committee

**DESIGN OF STUDY** **:** Analytical study

**PERIOD OF STUDY** **:** November 2006 to October 2007

**INCLUSION CRITERIA** **:** HCM cases was taken up based on echocardiographic documentation of a hypertrophied nondilated left ventricle (LV) in the absence of another cardiac or systemic disease that could produce the magnitude of hypertrophy evident at some time during the natural course of the disease as proposed by Dr. Maron B.J[3].

**EXCLUSION CRITERIA** **:** Left ventricular Hypertrophy due to other causes

Age less than twelve years

**CONSENT** **:** Informed consent was obtained from all those who participated in the study.

**METHODS:**

Selected socio-demographic, clinical and laboratory data were collected from the patients and recorded in a proforma.

Socio demographic data comprised of:

- age
- sex
- locality
- occupation

Clinical data comprised of:

Dyspnoea: Based on Newyork Heart Association Classification

Class I: HCM with no limitation of physical activity

No symptoms with ordinary exertion

Class II: HCM with slight limitation of physical activity

Ordinary activity causes symptoms

Class III: HCM with moderate limitation of physical activity

Less than ordinary activity causes symptoms

Class IV: Inability to carry out any physical activity without discomfort

Orthopnea

Paroxysmal Nocturnal Dyspnea

Exertional Chest pain

Palpitation

Syncope/Presyncope

Hypertension

Myocardial Infarction

Sudden Death in the Family members

Systemic examination:

Blood Pressure taken in Forearm in Sitting Posture

Pulse Rate: Rate, Rhythm, volume, Special Characters

Cardiac Murmurs

Other system involvement

Laboratory data included:

- Hb%
- Blood Sugar
- Blood Urea
- Serum Creatinine

**ECG:** Rate, rhythm, axis, QT interval, ST changes, T wave changes, Chamber Hypertrophy, arrhythmias, Major and Minor criteria for HCM as proposed by Charan et al[53]

**Echocardiography**

Imaging was done in the left lateral decubitus position using an ALOKA SSD 4000 with a multifrequency transducer equipped with Doppler tissue imaging software. Standard views for M mode and cross sectional studies were obtained. Standard techniques were employed for sizing the left ventricle and left atrium. The magnitude and distribution of left ventricular hypertrophy were assessed in the parasternal short axis plane by dividing the ventricle into four regions: anterior septum, posterior septum, lateral wall, and posterior wall. Wall thickness was measured at the levels of the mitral valve and the papillary muscles in each of the four segments. Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment. A semi quantitative point score of left ventricular hypertrophy (Wigle score) was calculated using a previously described method. To measure the Left ventricular mass the formula was LV mass = 1.04 *(IVST +PWT+LVDD)$^3$-(LVDD)$^3$. Ejection Fraction =(100*(LVEDD$^3$-LVESD$^3$))/LVEDD$^3$

Peak left ventricular outflow tract flow velocity was determined using continuous wave Doppler, and pressure gradients were calculated using the simplified Bernoulli equation. Transmitral left ventricular filling velocities at the tips of the mitral valve leaflets were obtained from the apical four chamber view using pulsed wave Doppler echocardiography. The transmitral left ventricular filling signal was traced manually and the following variables derived: peak velocity of early (E) and late (A) filling, and E/A ratio.

**Genetic Analysis**: Genetic Studies particularly mutations in sarcomeric gene myosin heavy chain were studied.

**CONFLICT OF INTEREST:**

There was no conflict of interest.

**QUESTIONNAIRE:**

Proforma has been included in the end of this material

**FINANCIAL SUPPORT:** Nil

**MAIN OUTCOME MEASURES:**

Analyzing various symptomology, clinical findings, and comparing with the Standard references.

**LIMITATIONS :** This study was based mainly on Echocardiography .Hence any false positive and false negative affects the inference of the study group.

**STATISTICAL ANALYSIS:**

Data were entered in Microsoft Excel spread sheet and analyzed utilizing the software - epidemiological information package 2002 (Epi Info 2002) - developed by centre for disease control and prevention, Alaska for World Health Organization. Range, mean, standard deviation and ‘p’ values were calculated using this package. Significance was considered if the ‘p’ value was below 0.05.

# RESULTS

Total number of patients attended Cardiology Department during our study period(Nov 2006-Oct 2007): 16680 cases.

Out of which twenty nine was found to have hypertrophic cardiomyopathy.

**Results obtained were**

**PREVALENCE:**

Prevalence of HCM among cases attending Cardiology Department was 1:575.

**AGE:**

**(Table 1) Age Distribution**

| Age in years | Cases | |
|---|---|---|
| | No. | % |
| Less than 20 | - | - |
| 20-29 | 10 | 34.5 |
| 30-39 | 3 | 10.3 |
| 40-49 | 4 | 13.8 |
| 50-59 | 7 | 24.1 |
| 60-69 | 4 | 13.8 |
| 70 & above | 1 | 3.5 |
| Total | 29 | 100 |
| Mean | 42.2 yrs | |
| S.D. | 15.4 yrs | |

Out of 29 patients, the mean age of presentation was 42.2 years with Standard Deviation of 15.4.

Lowest age of presentation was twenty years.

Oldest age of presentation was found to be seventy years.

Maximum number of cases in the range of 20-29 years

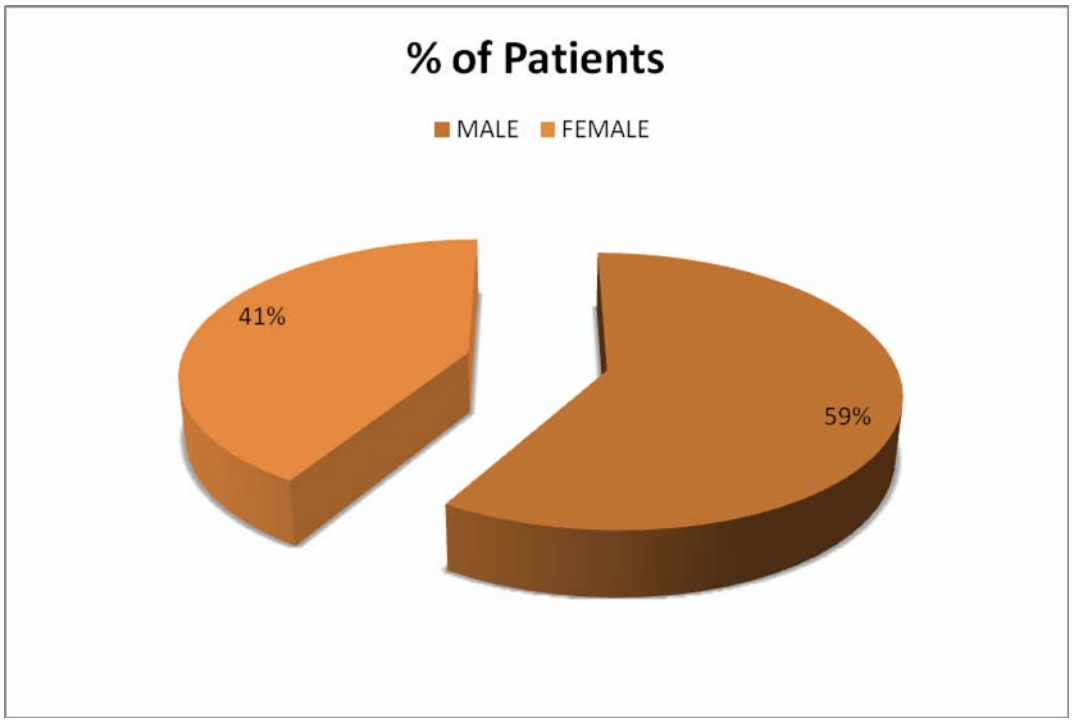
**GENDER:**

Out of the 29 cases

17 male

12 female

Graph 1



**SYMPTOMS:**

On analyzing various symptomology,

Dyspnoea found to be common presentation of cardiomyopathy present in 19(65.5 %) of the cases and 10 cases have no dyspnoea (Class I)

On break up Dyspnoea based on NYHA Classification 10 (34.5%)patients was in class I,11(37.9%) patients in class II,7 (24.1%)were in class III, 1(3.4%) was in class IV

**Graph 2**

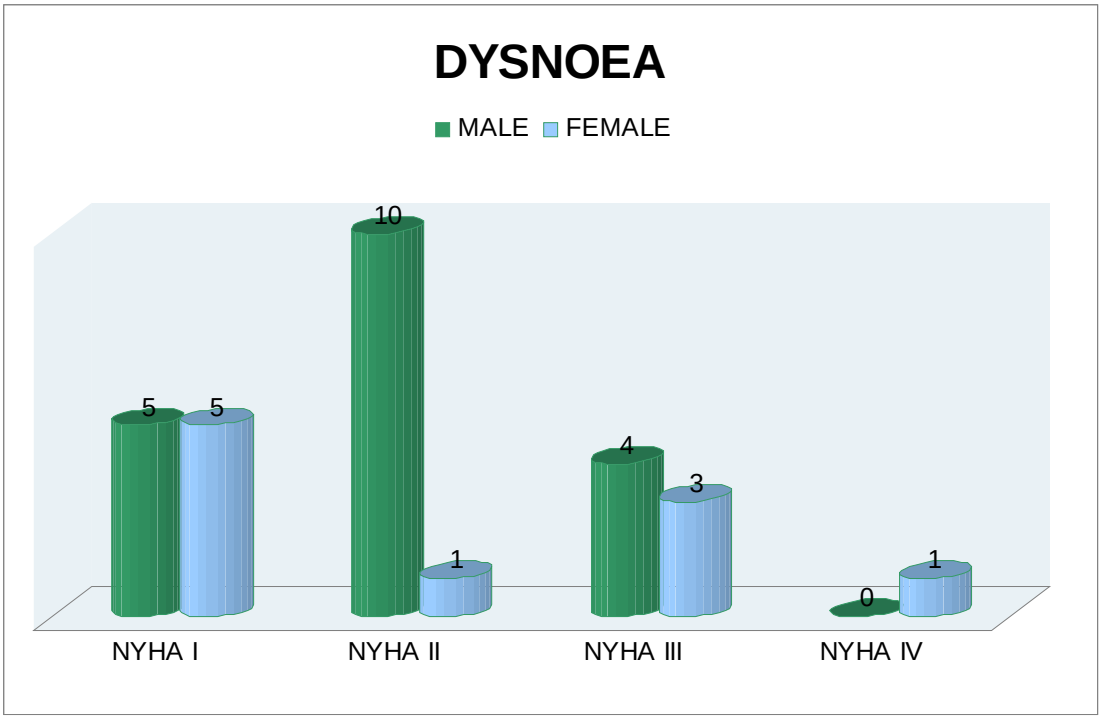


**Table 4**

| Other Symptoms | Cases | |
|---|---|---|
| | **No.** | **%** |
| **Orthopnea** | | |
| Present | 9 | 31 |
| Absent | 20 | 69 |
| **PND** | | |
| Present | 2 | 7.1 |
| Absent | 26 | 92.9 |
| **Chest pain** | | |
| Present | 12 | 41.4 |
| Absent | 17 | 58.6 |
| **Palpitation** | | |
| Present | 16 | 55.2 |
| Absent | 13 | 44.8 |
| **Syncope** | | |
| Present | 8 | 24.6 |
| Absent | 21 | 71.4 |

| Other Symptoms | Cases | |
|---|---|---|
| | No. | % |
| **Hypertension** | | |
| Present | 9 | 31 |
| Absent | 20 | 69 |
| **MI** | | |
| Present | 2 | 6.9 |
| Absent | 27 | 93.1 |
| **Sudden death in family** | | |
| a) First degree | 3 | 10.3 |
| b) Second degree | 3 | 10.3 |
| Total | 6 | 20.7 |
| No sudden death | 23 | 79.3 |

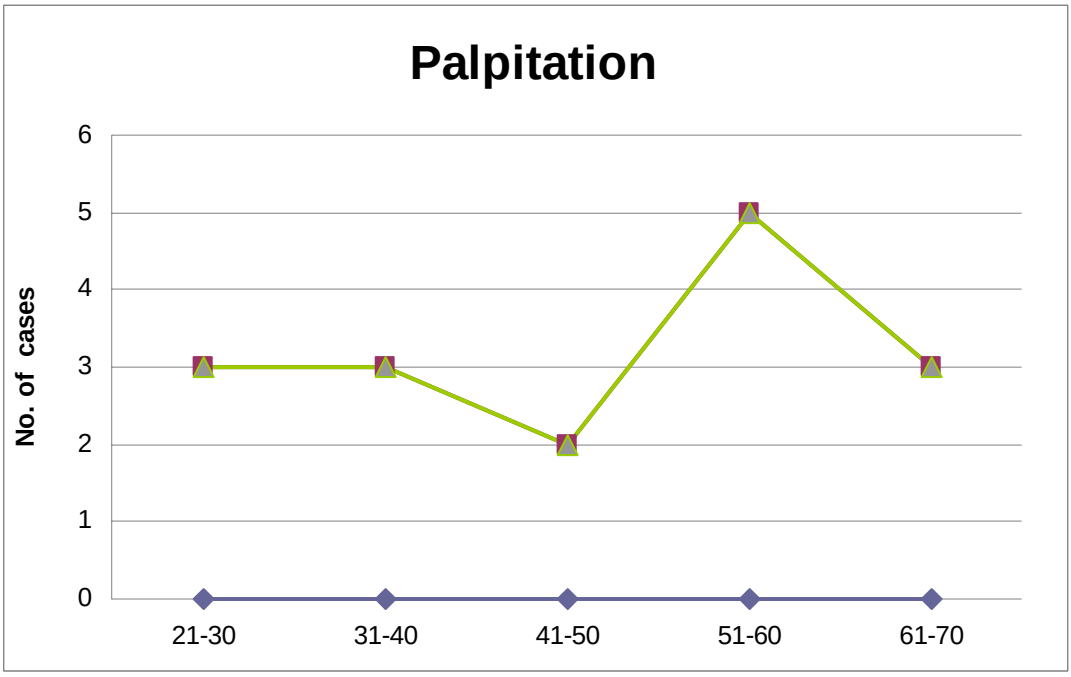
**CHESTPAIN:**

Twelve (41.4%) cases had chest pain, out of which two cases had no other symptoms. Out of female had higher percent age of chest pain compare to their male counter part (41.6% of the female cases)

**PALPITATION:**

Sixteen (55.2%) cases had palpitation, out of which two cases had no other symptoms

Graph - 3




**SYNCOPE:**

Eight (24.6%) cases had Syncope. In one case syncope alone was the presenting compliant.

**HYPERTENSION:**

Past history of Hypertension was present in nine cases.

**MYOCARDIAL INFARCTION:**

Two cases had past history of MI.

**SUDDEN DEATH IN THE FAMILY:**

Sudden death due to cardiac within 45 years was considered as sudden cardiac death(SCD). Positive history of sudden death in the family was present in six of our cases. First degree relative having sudden death in three of the cases.

**PHYSICAL EXAMINATION & LABORATORY INVESTIGATION:**

Table 4

| **Parameter** | **Mean** | **S.D.** |
|---|---|---|
| Systolic BP | 126.7 | 21.3 |
| Diastolic BP | 80.3 | 10.4 |
| Pulse | 77.5 | 22.4 |
| Hb% | 10.59 | 1.67 |
| Urea | 28.6 | 7.8 |
| Creatinine | 0.95 | 0.19 |
| Blood Sugar | 112.8 | 44.3 |

All the cases had positive clinical finding in the form of systolic murmur except two cases, hence insignificant for comparison.

Ten patients have anemia with hemoglobin of < 10gm%.

**ELECTROCARDIOGRAPHY:**

RATE and RHYTHM:

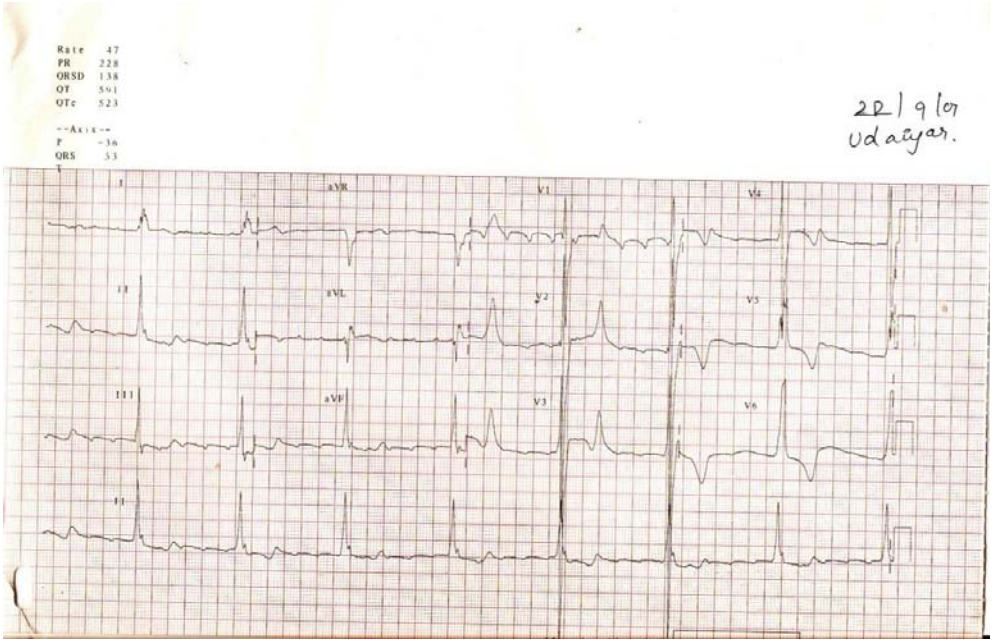
Twelve cases had Bradycardia in our study group. Sinus rhythm was present in 24 cases.

ARRHYTHMIA:

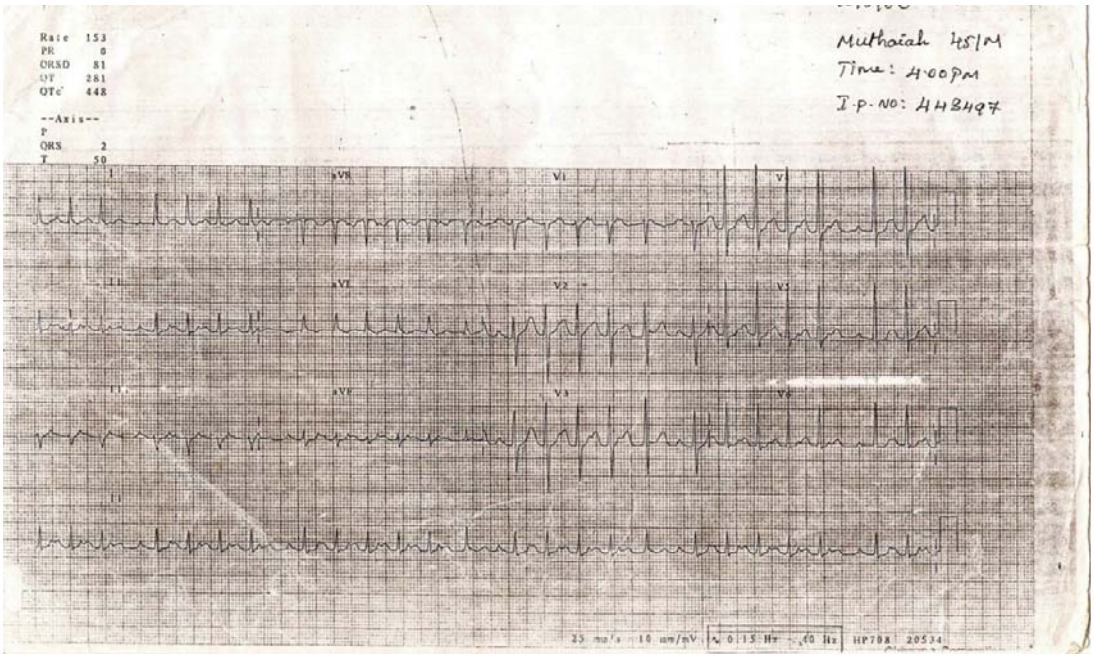
One case had atrial flutter with varying block.

Two cases had complete heart block.

FLUTTER WITH VARYING BLOCK



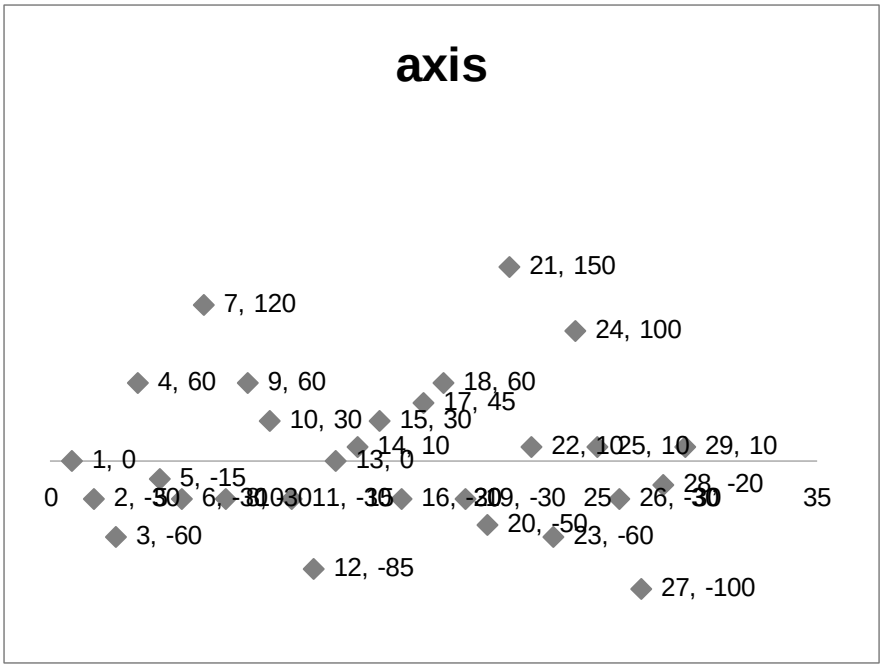

PAROXYMAL ATRIAL TACHYCARDIA WITH VARYING BLOCK

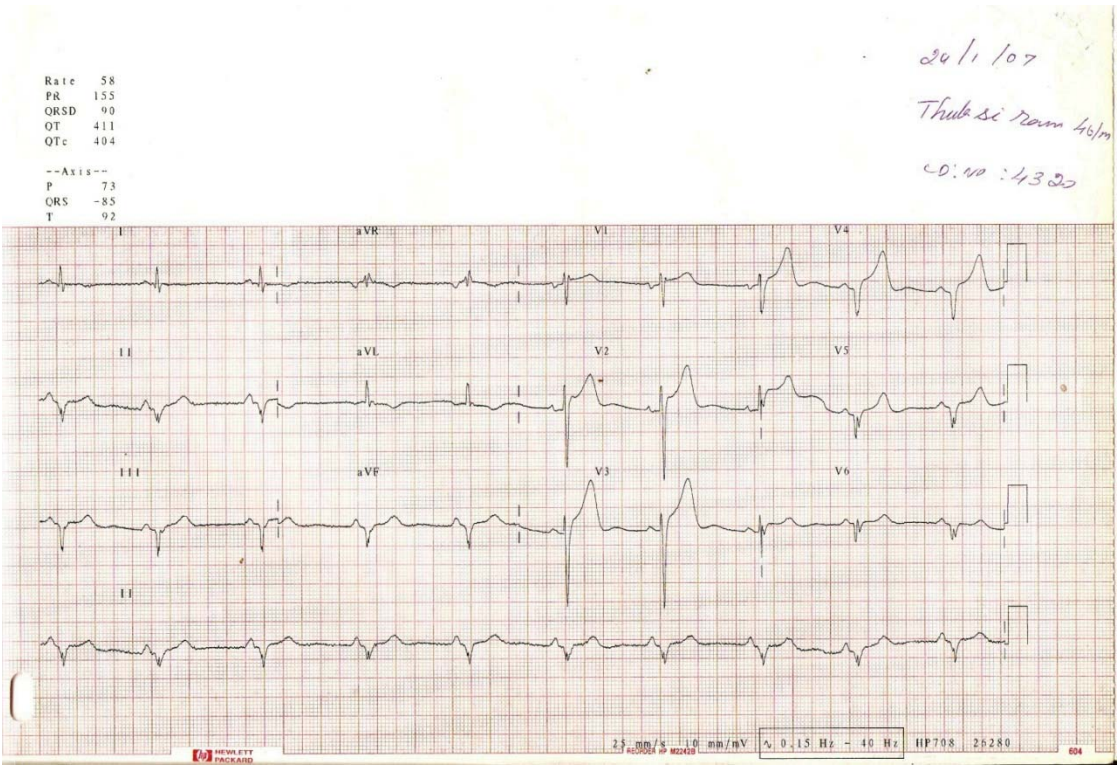



AXIS IN ECG:

Dispersion of cases against axis was shown in the graph.

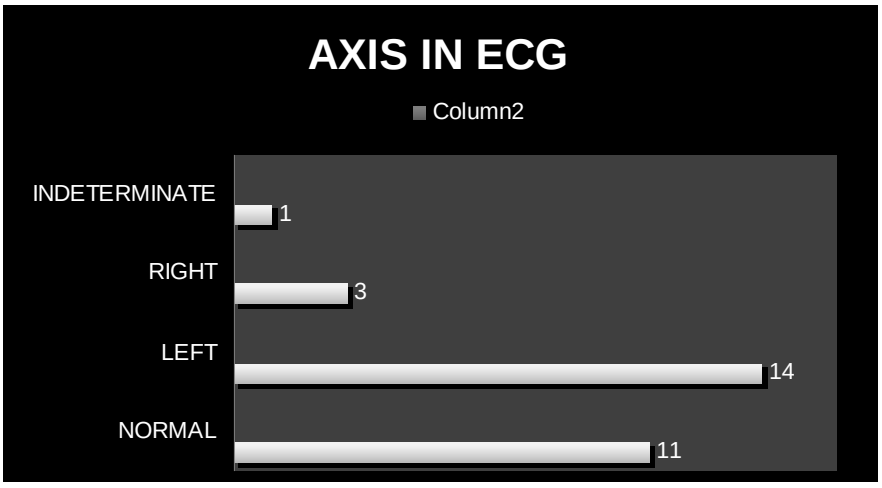
**Graph - 5**

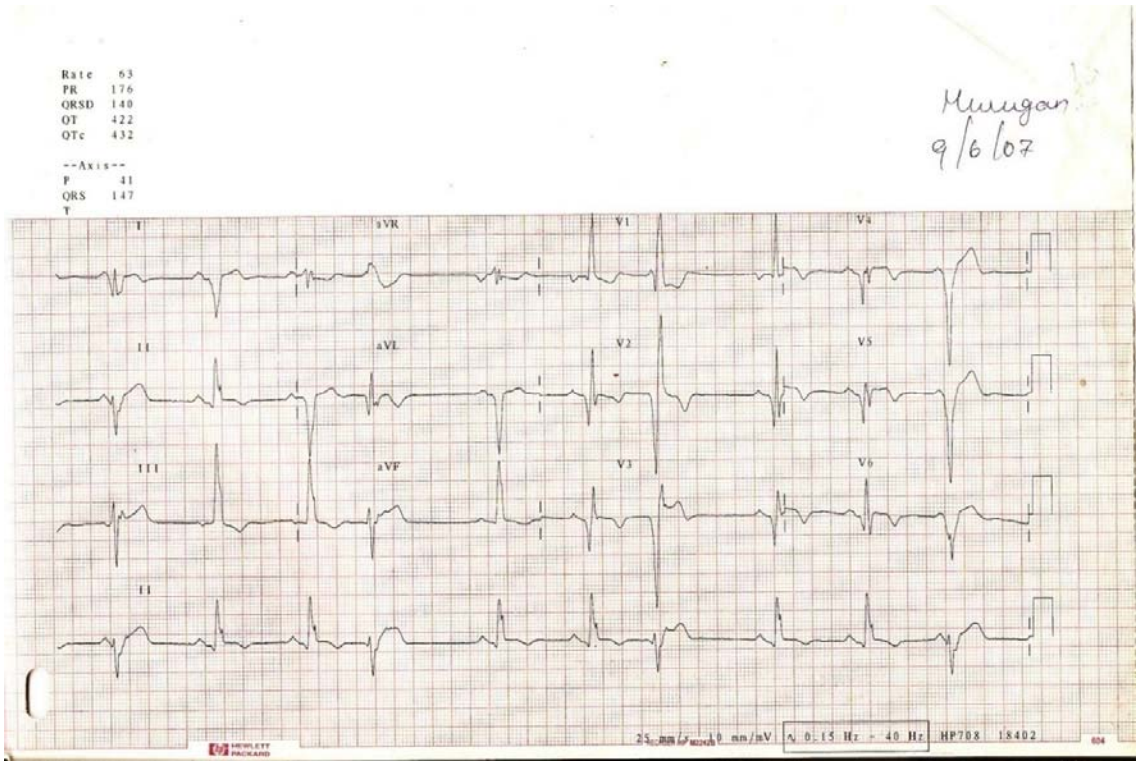





ECG showing Left Axis Deviation (- 85).

Mean Axis of our study cases was 6.33.Range was between 150 to 100.With 15 cases having left axis, three cases having Right Axis deviation.






CLASSICAL Q WAVE IN $V_1$ TO $V_6$

**MAJOR CRITERIA IN ECG[52]**

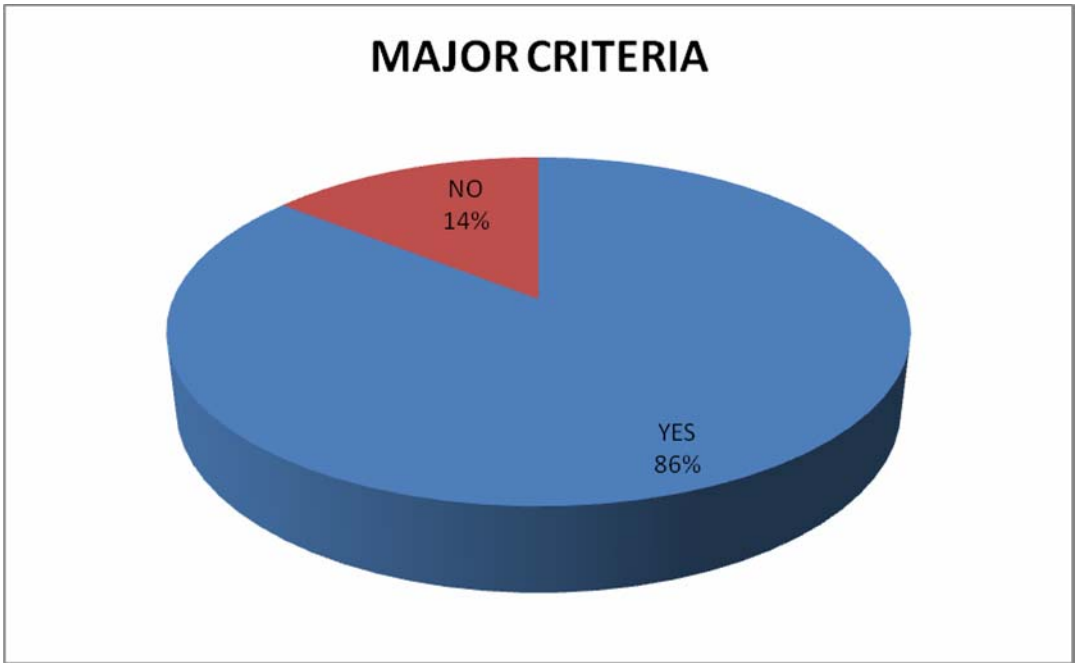
(1) Q waves >0.04 second in duration and/or >1/3 of the ensuing R wave in depth and present in at least two leads, or

(2) left ventricular hypertrophy assessed by a Romhilt-Estes score ≥4,[46] or

(3) repolarization alterations with marked T-wave inversion in at least two leads in the absence of bundle-branch block or hemiblock with or without ST-segment displacement under the isoelectric line.

In 24(86.2%) cases of our study, major criteria was positive.

Graph - 6




MINOR CRTITERIA IN ECG

Isolated left atrial enlargement assessed by a negative P wave in lead $V_1$ greater than -0.03 mV-second,[47]

short PR interval <120 ms,

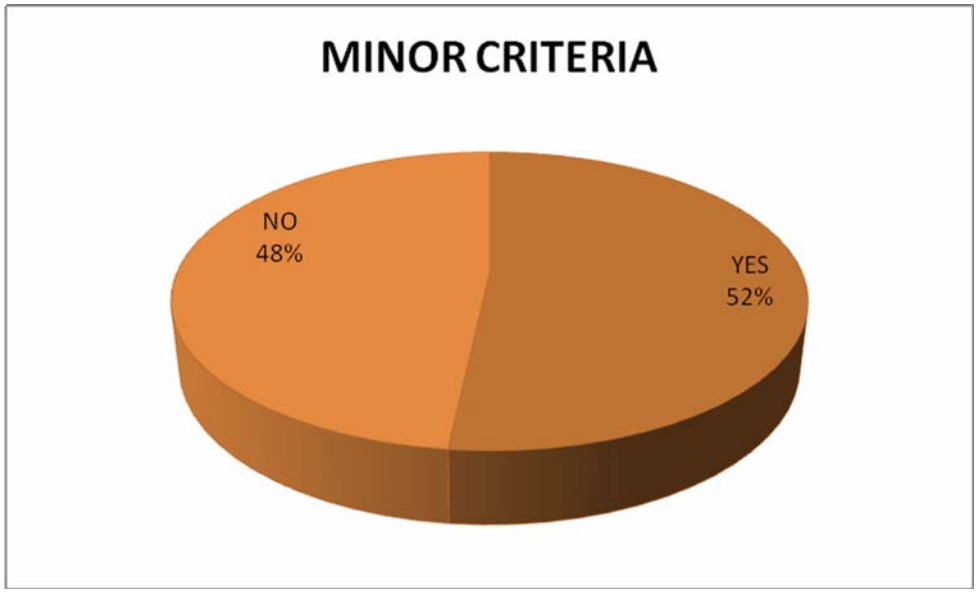
microvoltage assessed by a voltage <5 mV in each limb lead,

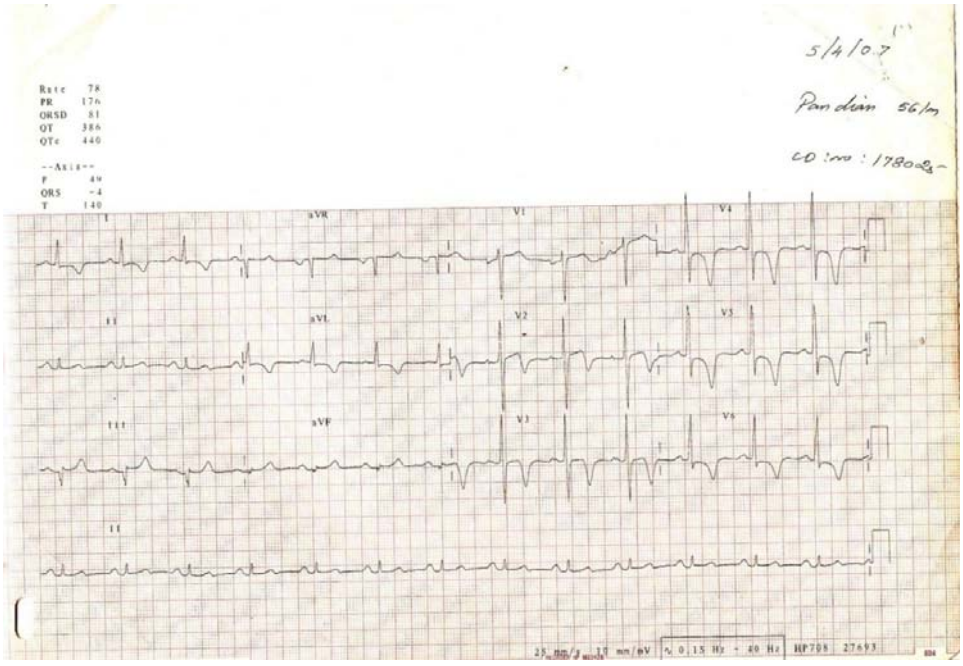
minor Q waves in at least two leads, or bundle-branch block or hemiblock.[48]

In 15(51.7%) cases of our study, minor criteria were positive.

On combining both major and minor criteria 100% of cases were positive.

**Graph - 7**



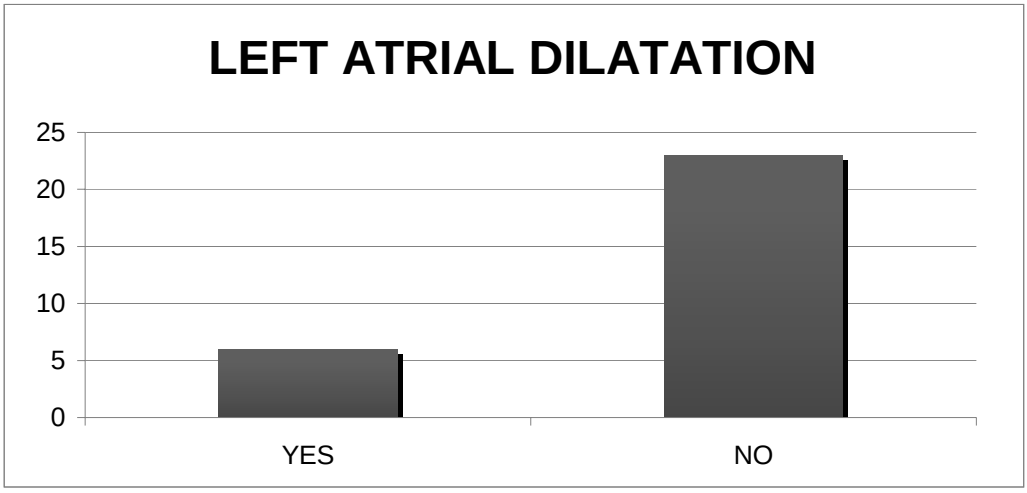



APICAL HCM

**LEFT ATRIAL ENLARGEMENT IN ECG**

Left atrial dilatation was present in six of our cases.

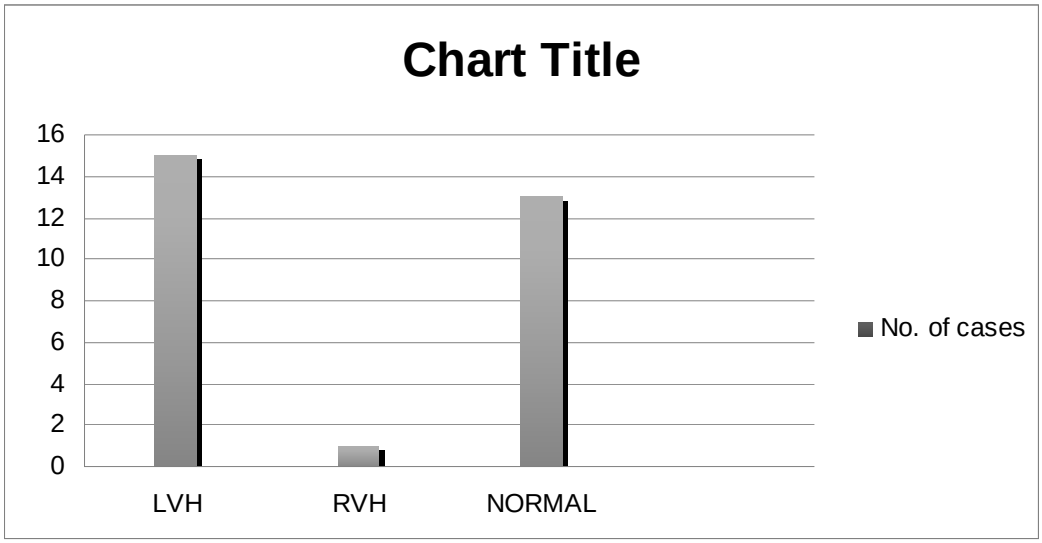
**Graph - 8**




**LEFT VENTRICULAR CHAMBER HYPERTROPHY IN ECG**

Fifteen of our patients had LVH with one case of both ventricular hypertrophy.

**Graph- 9**

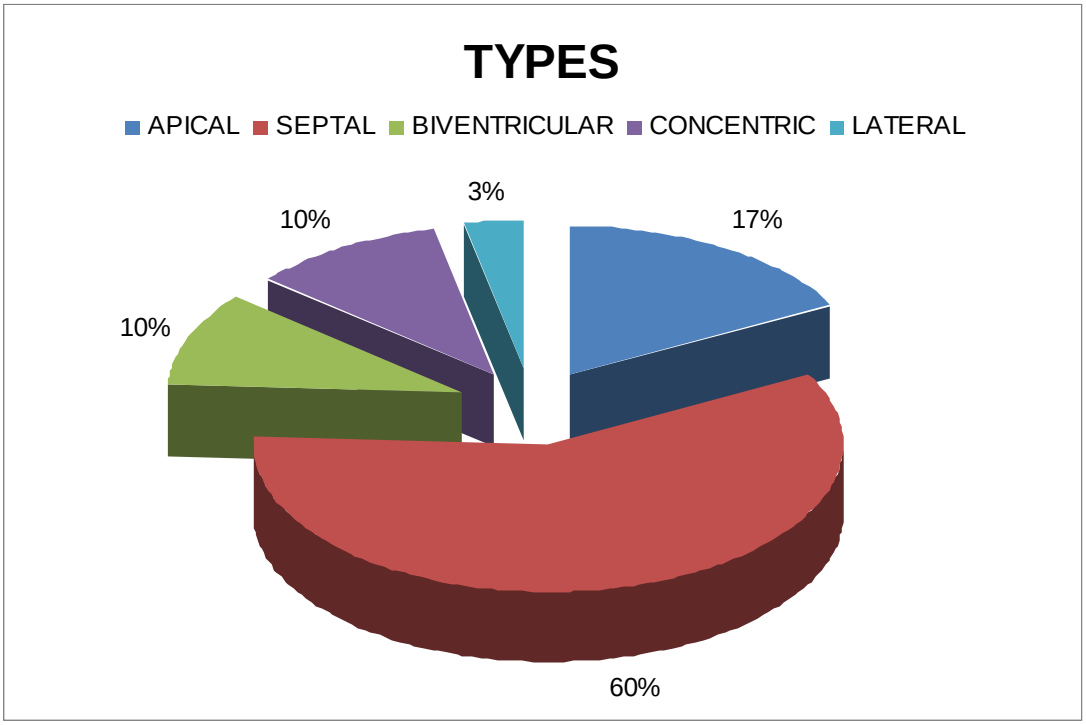


## ECHOCARDIOGRAPHY IN OUR STUDY

### TYPES OF HCM

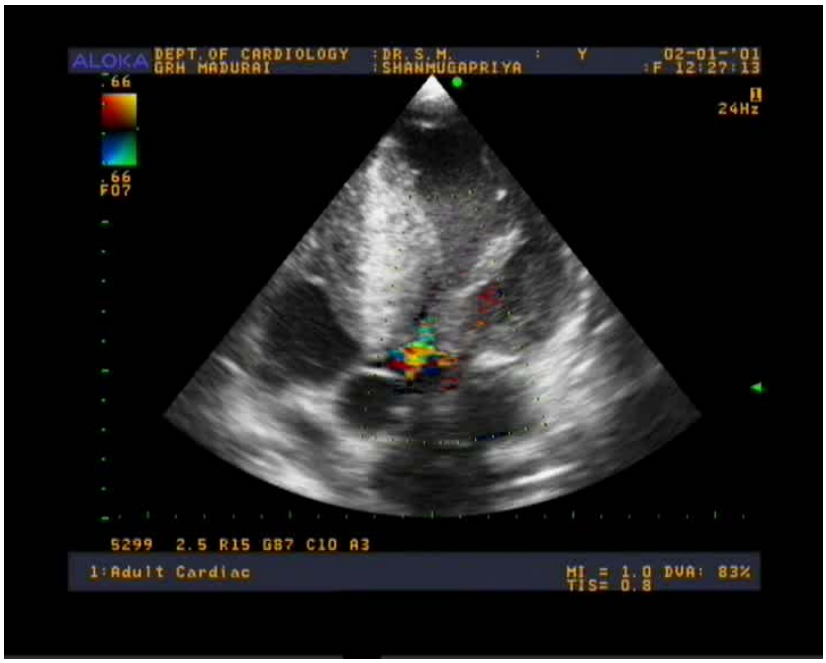
About 17 patients in the study group have asymmetric septal hypertrophy constituting 59%, Five cases had Apical HCM constituting 17%, three Biventricular 10%, Concentric HCM 10%, Lateral HCM of the study group

**Graph - 10**




septal wall thickness >13mm


Biventricular HCM



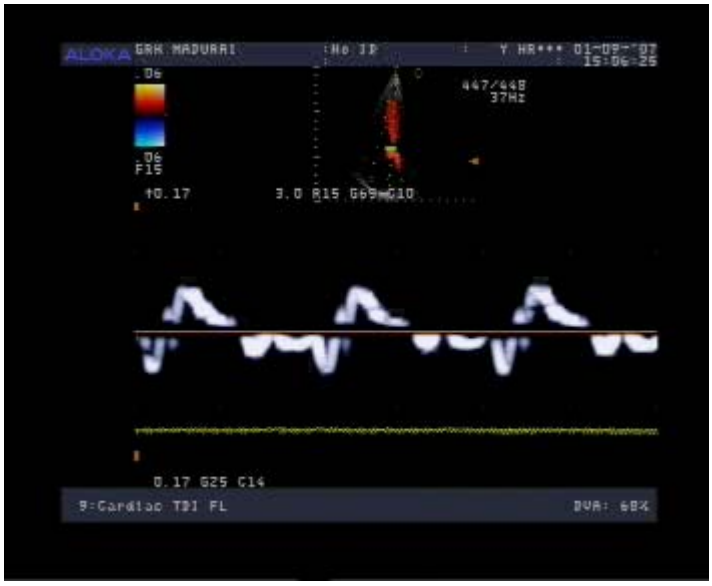

ECHO showing LVOT


Apical HCM .ECHO showing Measurements at Apex.

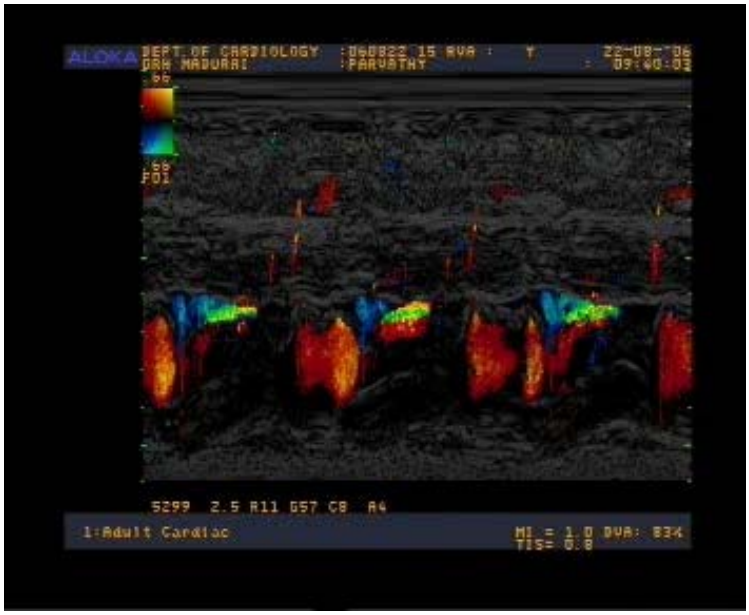
ECHO showing SAM



Concentric HCM




ECHO showing Tissue density Index

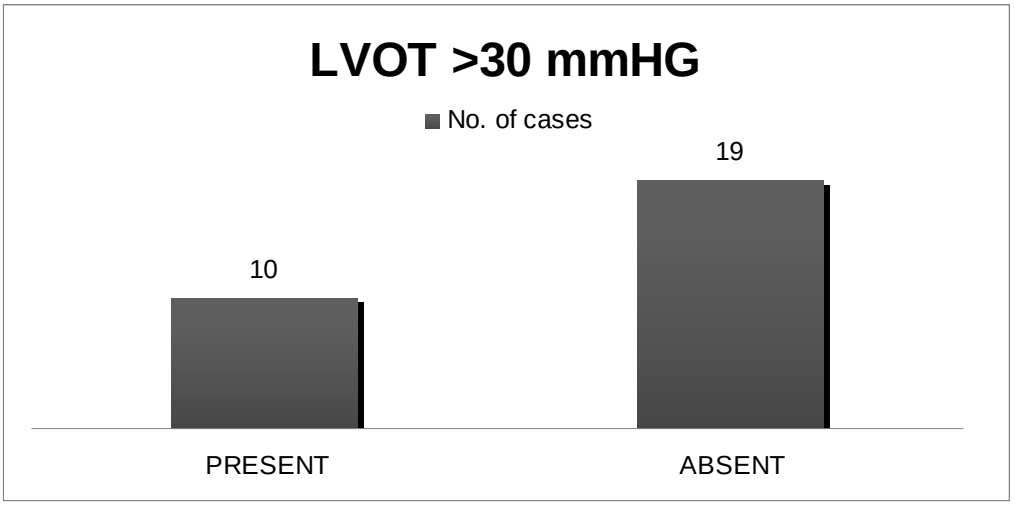



ECHO showing Colour Doppler

## LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

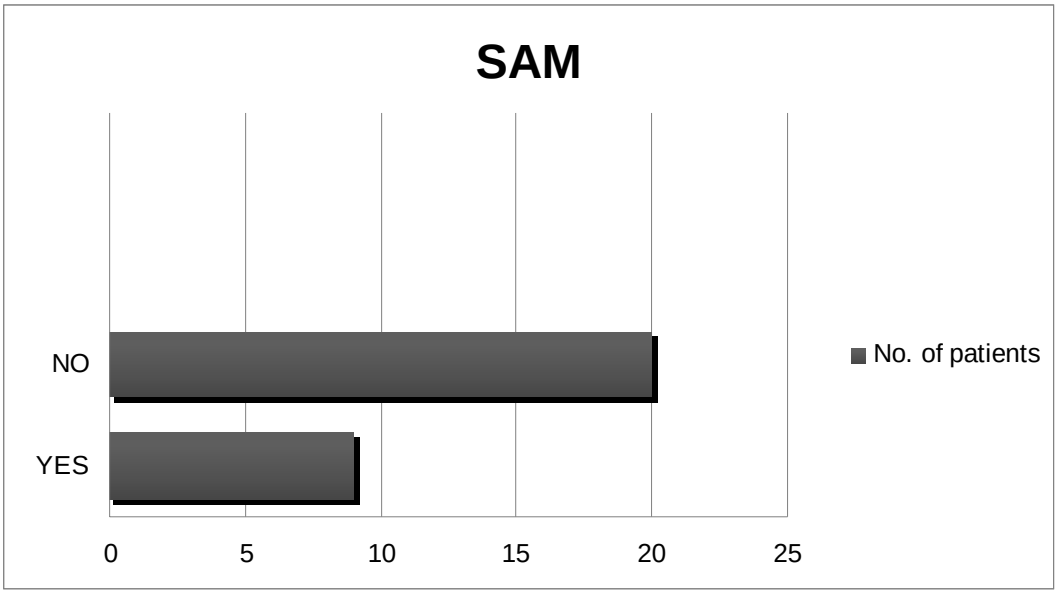
Ten cases of the study group have left ventricular outflow tract obstruction >30mmHg

**Graph - 11**




## SEPTAL ANTERIOR MOTION

**Graph - 12**



## Table 5

## BASE LINE CHARACTERSITCS OF THE STUDY CASES

| Parameter | Value | |
|---|---|---|
| | **Mean** | **S.D.** |
| LVID (d)(mm) | 43 | 9 |
| LVID (s)(mm) | 28.7 | 8.9 |
| LVEF % | 66.74 | 11.26 |
| IVS (d) (mm) | 19.2 | 7.1 |
| IVS (s) (mm) | 21.3 | 7.4 |
| LVPW (d) (mm) | 12.1 | 3.7 |
| LVPW (s) (mm) | 14.2 | 2.9 |
| LVM (grams) | 328.97 | 178.95 |
| MV (E) ($ms^{-1}$) | 0.58 | 0.26 |
| MV (A) ($ms^{-1}$) | 0.5 | 0.19 |
| TDI (S) ($ms^{-1}$) | 0.0717 | 0.02 |
| TDI (E) ($ms^{-1}$) | 0.0555 | 0.022 |
| TDI (A) ($ms^{-1}$) | 0.0703 | 0.021 |

**REGURGITATION LESION:**

In our cases, eleven had mitral regurgitation of Grade I - II, four cases of Tricuspid regurgitation, and two cases of aortic regurgitation.

**PULMONARY HYPERTENSION:**

Six cases of our study had pulmonary hypertension mild (2), moderate (3) and severe (1)

One cases was in moderate systolic LV dysfunction.

One of the cases was diagnosed to have Fredriech's Ataxia. Other incidental findings were Hypothyroidism, Pericardial effusion, Ovarian mass

**GENETIC ANALYSIS:**

Three cases of study group had deletion mutation in β-MHC genes. All the three cases had family history of sudden death at young age. On Echocardiographic screening of the Family members, two daughters of the case had early features of HCM but they were not fully evaluated,hence not takan up for study.

# DISCUSSIONS

**PREVALENCE:**

Average prevalence of HCM in world population was around 1:500 in general population. In our study prevalence rate was about 1:575 of patients attending cardiology department.But these cases are not the exact representative for General Population.

**AGE:**

On analyzing the age of the cases, Out of twenty nine cases, all the cases were above 20 years.Most of the cases in the study group was between 20-29 about 10 (34.5%) in number. Mean (SD) age was 42.2(15.4). Range was 20 - 70 years. Mean age in the world population was 42(15).

**SEX:**

In the our study group 17(58.6%) were male, 12(41.4%) were female. On comparing with the world incidence, Hypertrophic cardiomyopathy affects men and women equally and occurs in many races and countries, although it appears to be under-diagnosed in women, minorities, and under-served populations as reported by Elliot et al in Heart 2006.

**SYMPTOM ANALYSIS:**

On analyzing the symptoms **dyspnoea** was the most common symptoms in the study constituting 72.4%, most of them being NYHA class II dyspnoea. Female population reported late in the symptomatology. Incidence wise break up was Class I

– 34.5%, Class II – 37.9%, Class III – 24.1%, Class IV – 3.4%. Female cases constituting >50% of Class III-IV cases, signifying poor awareness among this population group.

A Study at St.George Hospital,London on evaluating 956 HCM cases dyspnoea was the presenting compliant in 72% with break up dyspnoea was Class I – 62.6%,Class II -34.5%,Class III-IV – 3.4%.(in other studies NYHA >III ranges from 33% in Brawnwald et al,19% in Maron et al,7% in Spirilo et al)[44]

Positive History of Excertional type of **chest pain** present in 12(41.4%) cases. Two cases have only chest pain as their complaint. Average incidence in the world literature being 28%.[44] the probable reason proposed was coronary ischemia hence specific instruction should be given for them to avoid severe exertion Positive History of **Palpitation** present in 16 (55.2%)cases. In Two cases ,it was the only positive symptoms. In one series palpitation reported was 26.3%.[44] It is one of the independent risk factors for Sudden Death.

**Syncope history** was positive in 8 (24.6%) cases of our study. Six cases of our study had more than two episodes of syncope. Syncope in HCM in world literature was around 16.5%.[44,]

In most of the studies quotes that Sudden Death increases in this set of population particularly having more than two episodes in six months .In patients younger than 45 years the sensitivity was rather low (35%), but the specificity was high (82%), with positive and negative predictive accuracies of 25% and 86%,

respectively.[45] Patients with obstructive HCM typically complain of dyspnoea, angina, and presyncope and /or syncope on exertion. The severity of symptoms on upright exertion do not necessarily correlate with the magnitude of obstructive pressure gradient measured in supine position.

Past history of **Hypertension** was reported in 9(31%) cases. Two cases with positive History of MI both inferior and anterior wall has been reported.

**FAMILY HISTORY OF SUDDEN DEATH:**

Family History of Sudden Death was reported in 6(20.6%) cases. Sudden death in the first degree relatives was three(10.3%). It is an independent risk factor for sudden death. A family history of one or more SCDs was associated with an increased risk of SCD in many series: sensitivity (42%), specificity (79%), positive predictive accuracy (28%), negative predictive accuracy (88%).[45]

On evaluating physical examination, most of the patients had Bradycardia (12cases),with mean (S.D) average of pulse rate being 77.5(22.4)/minute. On auscultation 27 cases had systolic murmur varying with exertion. Ten cases of our study had anemia with Hb% <10gm% which may aggravate the symptoms of chest pain

## ELECTROCARDIOGRAPHY:

All the study cases was evaluated with ECG, most common abnormal finding was the presence of LVH. Presence of Q wave in two consecutive leads was yet another coming finding. LAE was present in six of the cases. Major criteria in the form of LVH, Q waves in two consecutive leads, marked T wave inversion in two leads was positive in 25 cases hence ECG are of much useful tool along with Echo as a screening test. Abnormal Q waves, which may mimic myocardial infarction, and which at times reflect septal hypertrophy, are a feature of the ECG in HCM, as are sharply negative T waves, particularly in precordial leads V3–V5 (giant T negativity syndrome) typical of apical HCM as in our cases. Sensitivity of Major criteria was 86% which is comparable the earlier studies in literature (61%)[52]. Sensitivity of both Major and Minor criteria was 100%. It is extremely important to recognize that syncope/Presyncope may also result from atrial and ventricular arrhythmias at rest, even in non- obstructive HCM. Congestive heart failure is rarely seen in HCM in sinus rhythm. Hence these cases need continuous Holter ECG monitoring to rule out non sustained VT.

## ECHOCARDIOGRAPHY:

In our study, we looked for the presence of septal wall thickness, LVOT pressure gradient , septal anterior motion abnormality, any regurgitant lesion, mid ventricular obstruction, biventricular involvement, apical involvement.

On analyzing, 58.6 % of the cases had asymmetric septal Hypertrophy, 17.3 cases had apical hypertrophy which was found to be less than 10% in literatures except in Japan which needs further evaluation in our part the country. Three cases of Biventricular Hypertrophy has been reported in our study which were rarely mentioned in other series. Occurrence of concentric type of HCM was comparable to other series.

In our study ten cases had LVOT gradient of >30 mmHg. It is of clinical importance to distinguish between the obstructive or nonobstructive forms of HCM, based on the presence or absence of a LV outflow gradient under resting and/or provocable conditions . There is now widespread recognition that the subaortic gradient (30 mm Hg or more) and associated elevations in intra-cavity LV pressure reflect true mechanical impedance to outflow and are of pathophysiologic and prognostic importance to patients with HCM. Outflow obstruction is a strong, independent predictor of disease progression to HCM-related death (relative risk vs. nonobstructed patients, 2.0), to severe symptoms of New York Heart Association (NYHA) class III or IV.

In our study group 11 cases had mitral regurgitation of grade I-II. The mitral regurgitation that results from systolic anterior motion of the anterior mitral leaflet is directed posteriorly into the left atrium. If the mitral regurgitation is directed anteriorly or centrally, then additional abnormalities of the mitral valve such as abnormal papillary muscles or mitral valve prolapse should be suspected. In our study septal anterior motion was present in nine cases, which may be the reason for MR. Tran esophageal Echo was done three cases Transoesophageal echo Doppler studies are

particularly valuable in defining these additional mitral valve abnormalities and in distinguishing which type of obstruction is present in the left ventricle.

On genetic analysis three families had mutation for MHC genes, and on screening the family we could not able to detect HCM by echo except in one family . Two of her daughters had HCM. One interesting finding was that one of daughter had Apical while other had Septal HCM.

# CONCLUSION

Patients attending Cardiology Department between Nov 2006-Oct 2007 (16680 cases) were taken up for screening from which 29 cases were selected for my study based on inclusion criteria (a left ventricular (LV) wall thickness >/=15 mm and a nondilated cavity that was not associated with another cardiac disease and was sufficient to produce the magnitude of hypertrophy evident) for HCM and was analyzed clinically and genetically. **Age** of the cases was between 20 to 70 years (mean 42.2 +/- 15.4). Out of 29 cases 59% (n=17/29) were male and 41%(n=12/29) were female. **Dyspnoea** was the common symptoms(64.4%), Dyspnoea of Class III-IV accounts for one fourth the cases. Positive history of **syncope** was in one third of the cases(28.6%(n=8/29)) Positive family history of **sudden death** in 20.7%(6/29), **Electrocardiographic abnormalities** in most of the cases. Presence of **Septal anterior motion** in 31%(n=9/27), **LVOT obstruction >30mmHg** in one third of the cases, various **types of HCM** being Septal-58.6%, Apical-17.3%, Concentric-10.3%, Biventricular-10.3%.

In conclusion, **prevalence of HCM** was about 1:575 similar to most of studies reported , stressing the evidence that HCM is a relatively common genetic disease but these cases were not the exact representation of the general population.

History of Syncope and SCD in the family was similar to the general population in other studies.

LVH was the most common ECG findings in our study group.

Major Electrocardiographic changes were present in 90% of the cases much higher to other series (86.2% vs 61%).

The incidence of Apical and Biventricular HCM were higher compared with other series but it needs large multicentric trial for confirmation.

LVOT obstruction was present in 34.4% similar to other series.

SAM was present in one third of the cases much lower than other Literature.

From this study we can able risk stratify the cases based on Syncope, SCD in the family, Severe LVH, LVOT Obstruction >30mmHg. All these Factors are independent risk factors for Sudden Death, which needs early intervention either by drugs or by surgery.

The entire family member > 20 years has to be screened routinely.

Three cases of the study group had mutation in MHC gene considered to be malignant mutation. Further genetic analysis needed for detecting other deletion mutations.

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# PROFORMA

## CLINICAL PROFILE IN HYPERTROPHIC CARDIOMYOPATHY

Name : Age: Sex: IP no: CD no:

Address: Occupation:

History :

Breathlessness NYHA class

Orthopnea

PND

Chestpain duration

Palpitation

Syncope

Hypertension

Diabetes

MI

Smoking

Alcohol

Sudden death in family members

Examination :

JVP Carotids

PR

BP

Apical impulse Character

Heart sounds S1 S2 S3 S4 murmur

RS P/A CNS

Investigation:

Blood Hb%

Blood Urea

Serum Creatinine

Blood Sugar

ECG :

Echo :

TTE M Mode LVID(d) LVID(s) LVEF %

Thickness IVS d LVPW d LVM

s s

SAM

2 D

Doppler MV E AV LVOT

A

TV PV

Mid ventricular obstruction

RV involvement

Pulmonary hypertension

TDI S´ E´ A´

TEE

Genetic study:

| | | |
|---|---|---|
| **Breathlessness** | **1** | **NYHA class I** |
| | **2** | **NYHA class II** |
| | **3** | **NYHA class III** |
| | **4** | **NYHA class IV** |
| **Orthopnea** | **1** | **YES** |
| | **2** | **NO** |
| **PND** | **1** | **YES** |
| | **2** | **NO** |
| **Palpitation** | **1** | **YES** |
| | **2** | **NO** |
| **Chest pain** | **1** | **YES** |
| | **2** | **NO** |
| **Palpitation** | **1** | **YES** |
| | **2** | **NO** |
| **SYNCOPE** | **1** | **YES** |
| | **2** | **NO** |
| **HYPERTENSION** | **1** | **YES** |
| | **2** | **NO** |
| **MI** | **1** | **YES** |
| | **2** | **NO** |
| **MURMUR** | **1** | **YES** |
| | **2** | **NO** |
| | | |
| **SUDDEN DEATH IN THE FAMILY** | **1** | **FIRST DEGREE RELATIVE** |
| | **2** | **SECOND DEGREE RELATIVE** |
| | **3** | **NO SUDDEN DEATH** |
| **AXIS** | **1** | **LEFT AXIS** |
| | **2** | **RIGHT AXIS** |
| | **3** | **NORMAL AXIS** |
| | **4** | **INDETERMINATE** |
| **ST CHANGES** | **I** | **YES** |
| | **2** | **NO** |
| **QT CHANGES** | **1** | **YES** |
| | **2** | **NO** |
| **T WAVE INVERSION** | **1** | **YES** |
| | **2** | **NO** |
| **LEFT ATRIAL DILATATION** | **1** | **YES** |

| | | |
|---|---|---|
| | 2 | NO |
| VENTRICULAR HYPERTROPHY | 1 | LEFT |
| | 2 | RIGHT |
| | 3 | NORMAL |
| MAJOR CRITERIA | 1 | YES |
| | 2 | NO |
| MINOR CRITERIA | 1 | YES |
| | 2 | NO |
| SAM | 1 | YES |
| | 2 | NO |
| LVOT OBSTRUCTION | 1 | YES |
| | 2 | NO |
| MIDVENTRICULAR OBSTRUCTION | 1 | YES |
| | 2 | NO |
| RIGHT VENTRICULAR INVOLVEMENT | 1 | YES |
| | 2 | NO |
| PULMONARY HYPERTENSION | 1 | MILD |
| | 2 | MODERATE |
| | 3 | SEVERE |
| | 4 | NO |
| MR | 1 | GRADE I |
| | 2 | GRADE II |
| | 3 | NO |
| TYPES OF HCM | 1 | ASYMMETRIC SEPTAL |
| | 2 | APICAL |
| | 3 | CONCENTRIC |
| | 4 | LATERAL |
| | 5 | BIVENTRICULAR |

# ABBREVIATION & ANONYMS

| | | | |
|---|---|---|---|
| DM | Diabetes mellitus | TR | Tricuspid regurgitation |
| HCM | Hypertrophic cardiomyopathy | MR | Mitral regurgitation |
| HT | Hypertension | MI | Myocardial Infarction |
| IVS | Interventricular septum | NYHA | New York Heart Association |
| LVH | Left ventricular hypertrophy | PHT | Pulmonary hypertension |
| LVID (D) | Left ventricular Internal Diameter (diastole) | | |
| LVID(S) | Left ventricular Internal Diameter (systole) | | |
| LVPW | Left ventricular posterior wall | RVH | Right ventricular hypertrophy |
| LVOT | Left ventricular Outflow tract | SAM | Septal anterior motion |
| LVM | Left ventricular mass | SCD | Sudden cardiac death |
| LAE | Left Atrial Enlargement | SR | Sinus rhythm |
| MHC | Myosin Heavy Chain | VT | Ventricular Tachycardia |